Prospective Observational Study on Hematological Evaluation of Methotrexate and Dapsone in a Tertiary Care Hospital

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Abstract

Background: Methotrexate and Dapsone are widely used in the treatment of autoimmune and dermatological disorders. Both drugs are associated with potential haematological adverse effects, necessitating regular monitoring to ensure patient safety. However, real-world data on their haematological impact in Indian clinical settings remains limited.

Objective: To evaluate and compare the haematological profiles of patients receiving Methotrexate and Dapsone in a tertiary care hospital, and to identify the incidence and nature of associated haematological abnormalities.

Methods: This prospective observational study was conducted over a [insert duration] period in the Department of Dermatology/Medicine at Saisudha Hospital. Patients prescribed Methotrexate or Dapsone for various clinical indications were enrolled following informed consent. Baseline and follow-up haematological parameters, including hemoglobin, total and differential leukocyte counts, platelet counts, and other relevant indices, were recorded and analyzed.

Results: A total of 50 patients were included, with 23 receiving Methotrexate 27 receiving Dapsone. Haematological abnormalities such as anemia, leukopenia, and thrombocytopenia were observed in [insert percentage] of Methotrexate users and [insert percentage] of Dapsone users. The onset, severity, and reversibility of these abnormalities varied across individuals and were influenced by dose, duration, and comorbid conditions.

Conclusion: Both Methotrexate and Dapsone are associated with significant haematological changes that warrant routine monitoring. Early detection and timely intervention can prevent serious complications. This study highlights the importance of individualized patient evaluation and contributes to the optimization of drug safety in clinical practice.

Keywords: Methotrexate, Dapsone, Haematological toxicity, Adverse drug reaction, Prospective observational study, Tertiary care.

INTRODUCTION

METHOTREXTATE:

MTX is an antimetabolite. In 1951, Gunner and colleagues recognized that the folic acid antagonist aminopterin was effective for the treatment of psoriasis. Shortly after this observation, it was recognized that methotrexate (MTX, amethopterin), another folic acid antagonist, was also an excellent therapeutic agent for the control of psoriasis. Despite this discovery, it took nearly 20 years for the US Food and Drug (FDA) to approve MTX for use in psoriasis.

Only in the late 1980s was rheumatoid arthritis (RA) approved as another indication for the use of MTX. Despite large numbers of patients who have been treated with MTX, there remain many areas of controversy and confusion regarding the indications for, and the safety of this chemotherapeutic and immunosuppressive agent. Included among these controversies are:

(1) the criteria for selection of the psoriatic patient to receive MTX,

(2) the method of laboratory evaluation, and

(3) the need for liver biopsies and/ or noninvasive tests in surveillance.

With the approval of multiple new agents for the treatment of psoriasis, the use of MTX has declined; however, concomitant use of MTX with the tumor necrosis factor (TNF)-α antagonists is approved for patients with psoriatic arthritis and RA

❒ STRUCTURE :

MTX (4-amino-N10methyl pteroylglutamic acid) is a potent competitive antagonist (inhibitor) of the enzyme dihydrofolate reductase (DHFR).

It is structurally similar to folic acid, the natural substrate for this enzyme, differing from folic acid in only two molecular sites. The amino group in the 4-carbon position takes the place of a hydroxyl group, and a methyl group at the N10 Position substitutes for the hydrogen atom

❒ PHARMACOLOGY :

➢ Absorption and Distribution:

MTX can be administered orally, intravenously, intramuscularly, or subcutaneously, intrathecally. It is rapidly absorbed through the gastrointestinal (GI) tract, although peak levels occur more slowly (1 hour after ingestion) through oral route of administration. Although absorption of oral MTX may be incomplete and variable with doses greater than 15 mg this route of administration provides more reliable blood levels than parenteral administration.

Concurrent food intake, especially milk-basedmeals, may reduce bioavailability in children. However, in adults, the drug is unaffected by concurrent food ingestion. In addition, nonabsorbable antibiotics, such as neomycin may reduce the absorption of MTX significantly. The drug is well distributed throughout the body except in the brain, penetrating the blood-brain barrier poorly (thereby explaining why intrathecal MTX is needed in some chemotherapy regimens).

➢ Metabolism and Excretion:

Once absorbed, the level of MTX in the plasma has a triphasic reduction.

The first phase occurs rapidly 45 minutes and range distribution of the drug throughout the body.

The second phase of the plasma level reduction is represented by renal excretion and occurs over 2 to 4 hours. MTX is a weak organic acid excreted predominantly through the kidneys. Therefore, glomerular filtration and active tubular secretion are susceptible to drug interactions with other weak acids, such as salicylates, probenecid, and sulfonamides.

The third phase represents the terminal half-life and varies between 10 and 27 hours. This phase is thought to reflect a slow release of MTX, primarily bound to DHFR, from the tissues.

Approximately 50% of MTX is bound to plasma proteins, and the active portion of the drug is the free fraction (unbound) in the plasma

Thus, any drug that may increase the unbound MTX portion (such as sulfonamides and salicylates; see for others) may increase the beneficial tissue effects, as well as increasing the potential for toxicity.

MTX is actively transported into cells, rather than entering by diffusion. It was
previously thought that MTX is not substantially metabolized; however, evidence suggests that the drug is metabolized intracellularly, including by the liver, to polyglutamated forms.

These metabolites, also potent inhibitors of DHFR, are long-lived active compounds and are postulated to play a key role in MTX toxicity. Intracellular MTX polyglutamates have been proposed as potential biomarkers of MTX efficacy and toxicity in the treatment of inflammatory arthropathies.

Metabolism of action

Effects on Deoxyribonucleic Acid (DNA) Synthesis:

MTX competitively and reversibly binds to DHFR within 1 hour, with an affinity greater than that of folic acid. This prevents the conversion of dihydrofolate to tetrahydrofolate. Tetrahydrofolate is a necessary cofactor in the production of 1-carbon units, which are critical for the synthesis of purine nucleotides needed for DNA and ribonucleic acid (RNA) synthesis. A less rapid, but partially reversible, competitive inhibition of thymidylate synthetase also occurs within 24 hours after administration of MTX). Thus, the overall effect of MTX is inhibition of cell division, being specific for the S phase synthesis of the normal cell cycle.

The inhibition of DHFR can be bypassed by leucovorin calcium (N5 -formyl-tetrahydrofolate: folinic acid, citrovorum factor) or thymidine. Leucovorin, a fully reduced, functional folate coenzyme, bypasses the reaction catalyzed by DHFR. bypasses the reaction catalyzed by thymidylate synthetase. Thus, acute hematologic toxicity secondary to MTX can be reversed by high doses of folinic acid (leucovorin calcium) or thymidine.

T-cell Effects: The mechanism of action of MTX in psoriasis was originally thought to be caused by the suppression of hyperproliferation of keratinocytes. However [ref] Jeffs and colleagues demonstrated in an in vitro experiment that the effect of MTX on the proliferation of lymphoid cells is 1000 times greater than its effect on human keratinocytes. Thus, at concentrations reached in vivo, it is most likely that MTX acts via an immunosuppressive mechanism, rather than as an antiproliferative agent directed against the keratinocyte

↓

Inhibitions of migration and proliferations of activated t- cells

- **Folic Acid Effects on Methotrexate Therapy:**

The use of folic acid as a method of inhibiting MTX-induced GI AE and reducing the risk of pancytopenia is controversial. Multiple studies, primarily in the rheumatology literature, have suggested that folic acid administration does not impair the efficacy of MTX/ morgand colleagues have confirmed these clinical observations and demonstrated that administration of folinic acid, but not folic acid, reduces the efficacy of MTX. A recent review of the literature by Al-Dabagh and colleagues confirms a `reduction in AE of MTX in psoriasis patients receiving concomitant folic acid. However, they also noted weaker evidence supporting a reduction in efficacy. Therefore, folic acid supplementation is not universal and is often only routinely recommended if laboratory abnormalities or GI symptoms occur. Still other clinicians will give folic acid 1 mg daily (except day MTX given) in all patients.

* In general, this metabolic pathway is more important to the adverse effects of methotrexate (including drug interactions) than it is for drug efficacy. The fully reduced tetrahydrofolate is important for subsequent purine nucleotide synthesis.

A Folate (folic acid) is initially reduced to dihydrofolate by dihydropteroate synthetase.

B Dihydrofolate is further reduced to tetrahydrofolate by dihydrofolate reductase.

C **Methotrexate** inhibits this pathway through competitive inhibition of dihydrofolate reductase (DHFR).

D **Dapsone** and various **Sulfonamides** inhibit dihydropteroate synthetase, and thus, can amplify the inhibition of DHFR by methotrexate.

E **Trimethoprim** (including fixed combinations with sulfamethoxazole) also inhibits DHFR, and thus can amplify the inhibition of this pathway by methotrexate.

F **Folic acid** given in therapeutic doses essentially competes with methotrexate for DHFR, reducing the adverse effects of methotrexate by tetrahydrofolate production.

G **Folinic acid**, in a sense does an “end run” around the methotrexate inhibition of folate, serving as a fully reduced substrate for purine synthesis.

❒ DOSAGE

MTX is available as a 2.5-mg tablet or as 5.0-, 7.5-, 10-, and 15-mg tablets. MTX is also available in vials of sterile injectable solution ,which may be used for intramuscular, intravenous (IV), intrathecal, intraarterial, or subcutaneous administration (2 mL vials with 2.5 mg/mL to 25 mg/mL available). More recently, MTX is

now also available for subcutaneous injection via a prefilled autoinjector (7.5–25 mg doses which escalate by 2.5 mg increments), (7.5–30 mg doses, again escalating in increments of 2.5 mg).

❒ INDICATIONS :

MTX is approved for use by patients with malignancies, Including cutaneous lymphomas along with approval for psoriasis vulgaris, and RA. However, it is widely used in dermatology practice for many other conditions, including bullous disorders, autoimmune connective tissue diseases (collagen vascular disorders), pityriasis rubra pilaris (PRP), pityriasis lichenoid et varioliform is acuta (PLEVA), sarcoidosis, and miscellaneous unrelated diseases.

➢ US Food and Drug Administration-Approved Dermatologic Indications:

Psoriasis ,Sezary syndrome

➢ Off-label Dermatologic Uses

Proliferative Dermatoses ,Pityriasis rubra pilaris, Pityriasis lichenoid et varioliform is acuta, Reiter disease Immunobullous dermatoses like , dermatitis herpetitis forms (DH),Pemphis vulgaris ,Bullous pemphigoid and variants ,Epidermolysis bullosa acquisita ,Autoimmune Connective Tissue Diseases like Dermatomyositis , Subacute cutaneous lupus erythematosus ,Systemic lupus erythematosus , Systemic sclerosis , Morphea , Scleroderma □

Vasculitis—Neutrophilic Dermatoses : Leukocytoclastic vasculitis , Cutaneous polyarteritis nodosa , Kawasaki disease ,Pyoderma gangrenosum , Atopic dermatitis. **Other conditions include :** Sarcoidosis, Lymphomatoid papulosis mycosis fungoides,alopecia areota, Keratoacanthomas (intralesional)

□ **Psoriasis:**

The major clinical use of MTX in dermatology is in the therapy of psoriasis. The selection of the patient for the initiation of MTX therapy should be carefully considered. The benefits and risks of therapy, as well as

available alternative therapies, should be discussed fully before MTX initiation. In general, the patient who is considered to be a MTX candidate should have debilitating disease that either is uncontrolled by conventional methods or is not likely to respond to more conservative therapies.

Methotrexate is used to treat moderate to severe plaque psoriasis, psoriatic erythroderma, generalised pustular psoriasis, nail psoriasis, palmoplantar psoriasis, and psoriatic arthritis. Its use for the treatment of psoriasis was approved by the United States' Food and Drug Administration in 1972

The selection of the patient is made after the relative and absolute contraindications to the use of MTX are considered. In general, 75% to 80% of psoriatic patients treated with MTX respond, typically demonstrating an initial response within 1 to 4 weeks.

Full therapeutic benefit usually occurs within 2 to 3 months. A randomized trial demonstrated that 60% of MTX-treated patients reached a PASI (Psoriasis Area Severity Index)-75 score with 12 weeks of therapy at a dose of 15 to 20 mg weekly.

- **Autoimmune Connective Tissue Diseases**.

Patients with autoimmuneconnective tissue diseases (collagenvascular diseases), such as dermatomyositis, lupus erythematosus, and scleroderma (including localized subsets),can respond well to MTX. MTX has been extremely useful to adults and children with dermatomyositis or polymyositis who either do not respond to CS or who develop CS-related AE. The drug is very effective in the control of the muscle disease. In patients with cutaneous dermatomyositis, doses higher than those for psoriasis or RA are generally needed. Often, up to 30 to 35 mg of MTX weekly has been used for dermatomyositis patients; however, the average weekly dose we use is >15 mg weekly.

- **Vasculitis and Neutrophilic Dermatoses**

Systemic vasculitis, including polyarteritis nodosa an cutaneous polyarteritis nodosa, has been successfully treated with MTX.. Neutrophilic dermatoses, such as Behçet disease, pyoderma gangrenosum, and Sweet syndrome, may benefit from MTX therapy. The drug is most often used for these diseases as a means of sparing the patient from chronic high doses of CS.

Adverse effects

Hepato toxicity : The potential for hepatotoxicity in a patient treated with long-term MTX is an important consideration. Patient selection to avoid important risk factors (renal insufficiency, diabetes mellitus, obesity, and excessive alcohol intake) demonstrated a much lower incidence of this important complication, even at high cumulative doses. □

Pulmonary toxicity : Pulmonary toxicity, such as acute pneumonitis, can occur. This pulmonary toxicity is idiosyncratic, can occur with extremely small doses of MTX, and can be life-threatening if MTX is not stopped. In addition, some patients develop a more gradual pulmonary toxicity manifested by pulmonary fibrosis on chest x-ray.MTX induced pneumonitis has infrequently been reported in psoriasis patients. A chest x-ray should be done only if the patient develops symptoms suggesting pneumonitis. Or symptoms suggesting pneumonia □

Hematologic Effects :

Hematologic toxicity, such as pancytopenia, presents the greatest potential for loss of life as a result of MTX., the risk of pancytopenia was significantly reduced by routine folic acid supplementation. Be vigilant about potential drug interactions with MTX (particularly those involving trimethoprim/sulfamethoxazole (TMP-SMX) combinations, and to a lesser degree nonsteroidal anti-inflammatory drugs (NSAID) in combination with MTX; and Consider supplementing MTX treatment with 1 to 5 mg daily of folic acid (folate), regardless of whether the patient is experiencing nausea or other GI AE. Frequent complete blood counts (CBC) are important monitors for bone marrow toxicity. Should significant myelosuppression develop, the patient can be promptly treated with leucovorin (folinic acid), which can bypass the enzyme DHFR and allow normal cell division to resume. This procedure is commonly used for cancer patients treated with much higher MTX doses. Macrocytic indices without significant anemia are common with dermatologic dosage levels of MTX. This finding is not usually of any clinical significance.

- **Gastrointestinal Effects:** Nausea and anorexia are common AE to MTX. Diarrhea, vomiting, and ulcerative stomatitis are less frequently observed. The presence of ulcerative stomatitis or severe diarrhea requires cessation of the MTX therapy.
- **Renal Effects :** High-dose therapy (i.e., 50–250 mg/m2 intravenously; dosages used only in chemotherapy for malignant disease) may lead to renal toxicity
- **Other Adverse Effects :**
  - Alopecia
  - Hyper pigmentation
  - Toxic epidermal necrolysis
  - Ulceration in psoriatic plaque
  - Abdominal pain
  - Radiation recall syndrome

□ **Contraindications**

- Pregnancy
- Lactation

- Hepatic disease : active hepatitis , cirrhosis , liver disease
- Hematological abnormality

❒ Monitoring Guidelines

□ General Issues and Risk-Factor Assessment.

Before the first dose, a thorough evaluation of the patient should be completed. The pretreatment MTX evaluation begins with a thorough history and physical examination. This evaluation assists the physician to identify patients at increased risk for various important MTX adverse events (AE) □

Examination :

- Careful history and physical examination
- Identification of patients at increased risk for toxicity
- Recording concomitant medications that may interact with methotrexate

Laboratory :

- Complete blood count (CBC) and platelet counts
- Liver function tests (especially transaminases)a
- Serologic tests for hepatitis B, C
- Renal function tests: blood urea nitrogen, creatinine.
- Human immunodeficiency virus (HIV) testing in patients at risk for acquired immunodeficiency syndrome (AIDS)
- CBC, platelet count and liver function tests 5–6 days after ‘test dose’. Every 1–2 weeks for 2–4 weeks ,1–2 weeks after dose escalations acquired immunodeficiency syndrome (AIDS), a human immunodeficiency virus (HIV) antibody determination should be part of the screening. The type of renal function testing is a critical issue in elderly patients. Patients over 50 years of age, the serum determinations of the blood urea nitrogen and creatinine may not be sufficient.

In particular, the serum creatinine levels are not as reliable in older individuals with relatively low muscle mass. Reliable measurement of creatinine clearance is often difficult.

Liver Biopsy.

Liver biopsy

- Pretreatment liver biopsy not necessary in low-risk patient.
- First biopsy at 3.5 to 4 g total dose of methotrexate
- Subsequent biopsies after each 1.5 g accumulated methotrexate dose

Consider baseline liver biopsy in higher risk patients, such as those with NASH, obesity and/or hyperlipidemia Follow-up.

MTX dose before performing a 'baseline' liver biopsy on relatively low-risk patients. The need for repeated liver biopsies is based on the total dose taken by the patient. The cumulative dose should be periodically calculated and recorded in the patient's medical record to more effectively deal with the discussion of the need for a liver biopsy.

Biopsy grade	Liver histopathology	Remarks
I	Normal ,mild fatty and portal inflammation	MTX can be given
II	Moderate to severe fatty infiltration and portal infiltration	MTX can be given
IIIA	Mild fibrosis	MTX can be given but repeat biopsy after 6 months .
IIIB	Moderate to severe fibrosis	MTX cannot be given
IV	Cirrhosis	MTX cannot be given

❒ **Laboratory Monitoring:**

The patient should be monitored closely during the initial phases of therapy with frequent CBC (usually within 1–2 weeks after beginning therapy or escalating the dose), liver function panels, and serum creatinine measurements during the initial phase of therapy, regardless of the disease for which MTX is being used.

If the white blood cell count (WBC) is less than 3500/mm3 , the platelet count is less than 100,000/mm3 , or there is an increase over twice the upper normal value for liver transaminase levels, discontinue or reduce the dosage of MTX □ **Therapeutic Guidelines:**

Once plan is made to start MTX , dose and route have to be considered.

Oral weekly doses are tolerated

If not tolerating , parenteral (IM) route can be tried .

Weekly dose schedule :

Single weekly dose

It should be given three times in a day .

Initial dose schedule :

Start with 5- 10 mg test dose

Escalate to 2.5 – 5 mg / week to a maximum of 30 mg /week Taper by 2.5 mg /week to lowest possible dose that controls disease.

Toxicology:

Common organ system toxicity associated with high dose methotrexate:

Dermatologic	Erythema multiforme Steven – Johnson syndrome
Gastro intestinal	Nausea, vomiting, diarrhea and mucositis
Hematologic	Myelosuppression, neutropenia, thrombocytopenia.
Hepatic	Hepatic fibrosis
Neurologic	Encephalopathy, seizures, headaches Transient blindness
Pulmonary	Pneumonitis
Renal	Acute kidney injury

Medication counselling:

- Counsel female patient of reproductive potential to use effective contraception during therapy and for 6 months after the final dose
- Warn male patient with female partner of reproductive potential to use effective contraception during therapy and for at least 3 months after the final dose
- Instruct patient to avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause dizziness and fatigue
- Side effects may include stomatitis/mouth sores, headache, bronchitis, thrombocytopenia, alopecia, photosensitivity, and “burning of skin lesions
- Advise patient to immediately report symptoms of myelosuppression or serious infection
- Warn patient to report symptoms of organ toxicity, including gastrointestinal, hematologic, hepatic, neurologic, pulmonary, and renal
- Counsel patient to report symptoms of dermatologic reactions and to avoid excessive sun exposure and use sun protection measures
- Teach patient proper technique and placement of injections

- Advise patient prescribed a once weekly regimen that dose should be administered as directed and that mistaken daily use has led to fatal toxicity
- Tell patient to avoid alcohol during treatment
- Counsel patient to avoid live vaccines during treatment
- Instruct patient on high-dose methotrexate to avoid aspirin, NSAIDs, and proton pump inhibitors.

DAPSONE

INTRODUCTION:

- Dapsone is a sulfone with anti-inflammatory immunosuppressive properties as well as antibacterial and antibiotic properties.
- Dapsone is the principal drug in a multidrug regimen recommended by the World Health Organization for the treatment of leprosy.
- As an anti-infective agent, it is also used for treating malaria and, recent Pneumocystic carinii pneumonia in AIDS patients.
- Dapsone is absorbed rapidly and nearly completely from the gastrointestinal tract. Dapsone is distributed throughout total body water and is present in all tissues.
- However, it tends to be retained in skin and muscle and especially in the liver and kidney: traces of the drug are present in these organs up to 3 weeks after therapy cessation.
- Dapsone acts against bacteria and protozoa in the same way as sulphonamides, that is by inhibiting the synthesis of dihydro folic acid through competition with para-aminobenzoate for the active site of dihydropteroate synthetase.
- The anti-inflammatory action of the drug is unrelated to its antibacterial action and is still not fully understood.
- A sulfone active against a wide range of bacteria but mainly employed for its actions against mycobacterium leprae.
- Its mechanism of action is probably similar to that of the sulfonamides which involves inhibition of folic acid synthesis in susceptible organisms.
- It is also used with pyrimethamine in the treatment of malaria.

❒ **TREATMENT GIVEN FOR**: Acne vulgaris

Leprosy Dermatitis herpetiformis

❒ **MANAGEMENT FOR:** Pemphigus vulgaris

Relapsing polychondritis.

❒ **PHARMACOKINETICS :**

- **Bioavailability -**:70 to 80% follow ing oral administration.
- **Protein binding** i 70 to 90%.
- **Metabolism:**

Hepatic, mostly CYP2E1-mediated. However products below to view reaction partners. **Route of elimination:** Renal. **Toxicity:** Overdosage might be expected to produce nasal congestion, syncope, or hallucinations. Measures to support blood pressure should be taken if necessary.

- **Chemistry of sulfones:**

Dapsone (4-4′-diaminodiphenylsulfone, DDS) is structurally the simplest of the sulfones, all of which share the characteristic structure: a sulphur atom linking to two carbon atoms.

- **Absorption:**

Orally ingested dapsone is absorbed readily from the gastrointestinal tract with bioavailability of more than 86%. Absorption is reduced in severe leprosy. The disubstituted sulfones, such as sulfoxone, are poorly absorbed after oral administration, and large amounts are excreted in the faeces. In healthy volunteers, after 100 mg of oral dapsone, peak serum dapsone concentrations between 1.10 and 2.33 mg/L were reached within 0.5 to 4 hours. The elimination half-life ranged from 12 to 30.

- **Antimicrobial action:**

As an antibiotic, dapsone acts in the same way as sulfon amides, inhibiting the synthesis of dihydro folic acid through competition with *para*-aminobenzoate for the active site of dihydropteroate synthetase. Therefore dapsone inhibits the growth of microorganisms that are dependent on endogenous folic acid synthesis.

- **Anti-inflammatory action:**

Dapsone is effective in dermatoses with abnormal neutrophil accumulation, through many potential mechanisms. Dapsone interferes with neutrophil chemotactic migration and β2.

- **Food Interactions:**

Take with or without food. The absorption is unaffected by food. In their 60-year history, dapsone have been used as both antibacterial and antiinflammatory agents. Dapsone has been used successfully to treat a range of dermatologic disorders, most successfully those characterized by abnormal neutrophil and eisnophil accumulations

- **Clinical indications :**

Dapsone is both an antibiotic and an anti-inflammatory agent. It is bacteriostatic against Mycobacterium leprae and is an essential component of leprosy treatment. It has also been used successfully to treat Actino-

mycetoma in prophylaxis and treatment of Pneumocystis carinii pneumonia (PCP) and for malaria. As an antiinflammatory agent, dapsone has been used to treat many skin diseases characterized by the abnormal infiltration of neutrophils or eosinophils

Adverse effects:

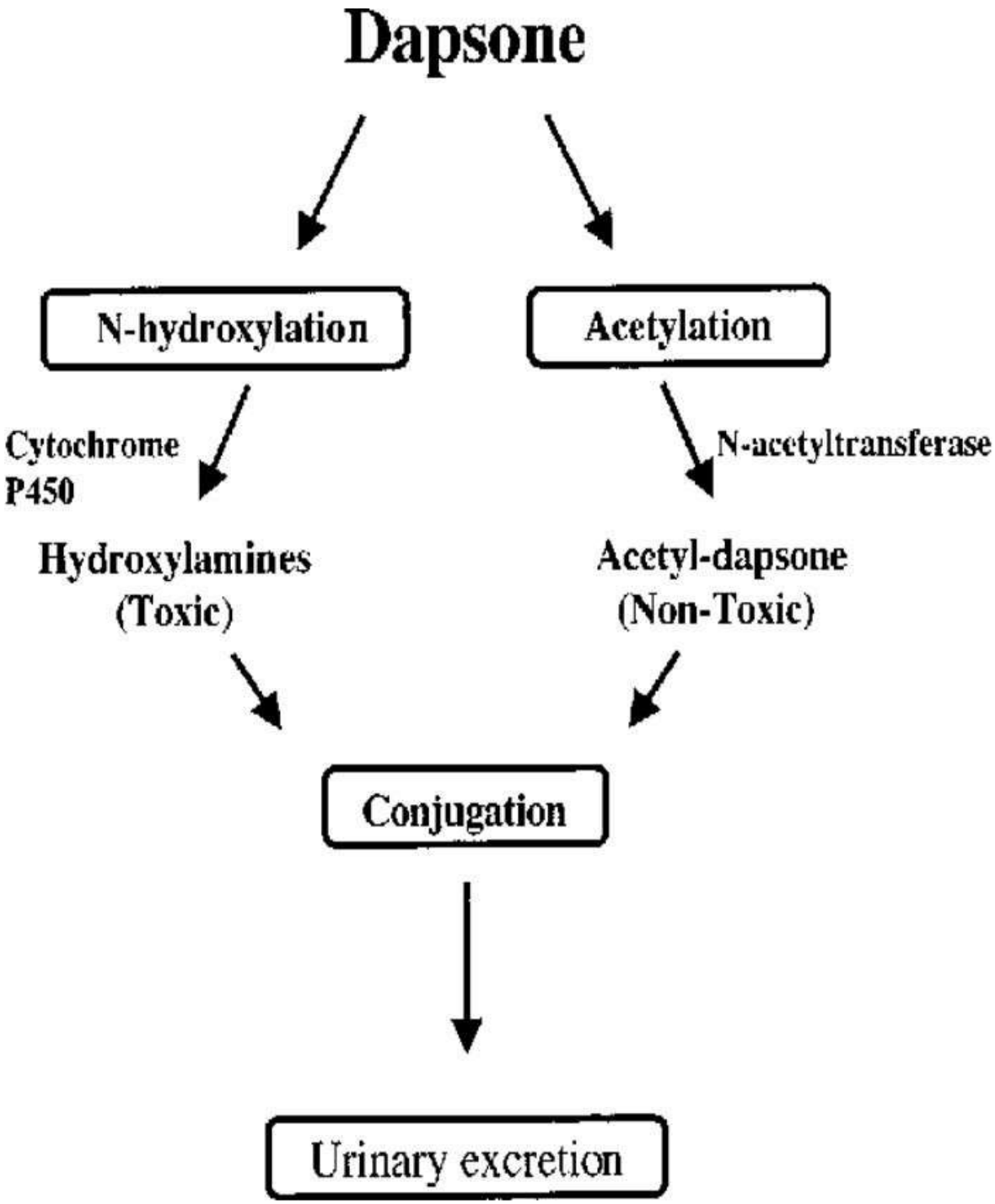
Overall, the risk of dapsone-dependent side effects is very low if the plasma concentration is below 5 mg/L. Although the therapeutic range for leprosy was estimated to be 0.5 to 5 mg/L, the ranges for other indications are not known. Metabolism of dapsone by cytochrome P-450 to hydroxyl amines is responsible for some dapsone side effects including methemoglobinemia, haemolysis, and fatal agranulocytosis, but the mechanism by which hydroxyl amines cause these side effects is unclear.

- **How to increase tolerance to dapsone:**

Use of a metabolic inhibitor such as cimetidine to reduce hepatic oxidation of dapsone to hydroxylamine has successfully decreased its adverse effects. Methaemoglobin formation in the presence of cimetidine was maintained at 30% below control levels for almost 3 months, and the incidence of reported side effects such as headache and lethargy were significantly reduce pain. Long-term concurrent cimetidine administration increased plasma dapsone levels without increased haemolysis.

- **Use during pregnancy and lactation:**

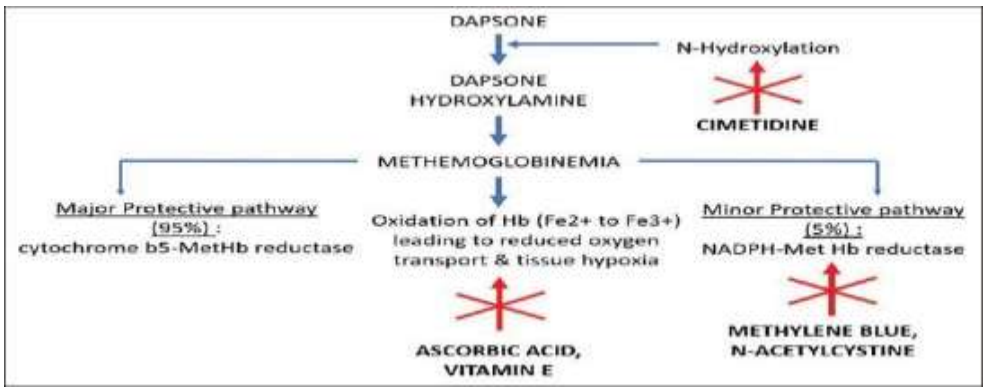
Pregnancy may be a trigger of leprosy and other dermatologic diseases because of the changes in cell-mediated and humoral immunity during gestation. First appearance of leprosy, reactivation of the disease, and relapse in “cured” patients are likely to occur particularly in the third trimester of pregnancy. Because up to 20% of children born to mothers with leprosy may experience leprosy by puberty, pregnant women with leprosy require treatment.



❒ **MECHANISM OF ACTION** :

Pathophysiology:

Dapsone exerts its antimicrobial action by inhibiting bacterial and folate synthesis. In addition, the drug demonstrates anti-inflammatory effects. Linear IgA bullous dermatosis, chronic bullous dermatosis of childhood, bullous systemic lupus erythramatous.



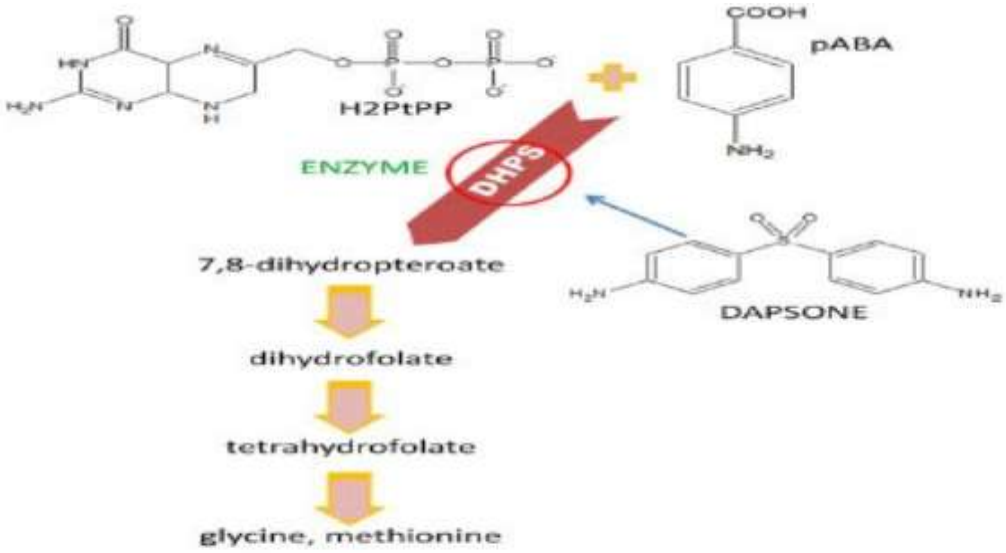
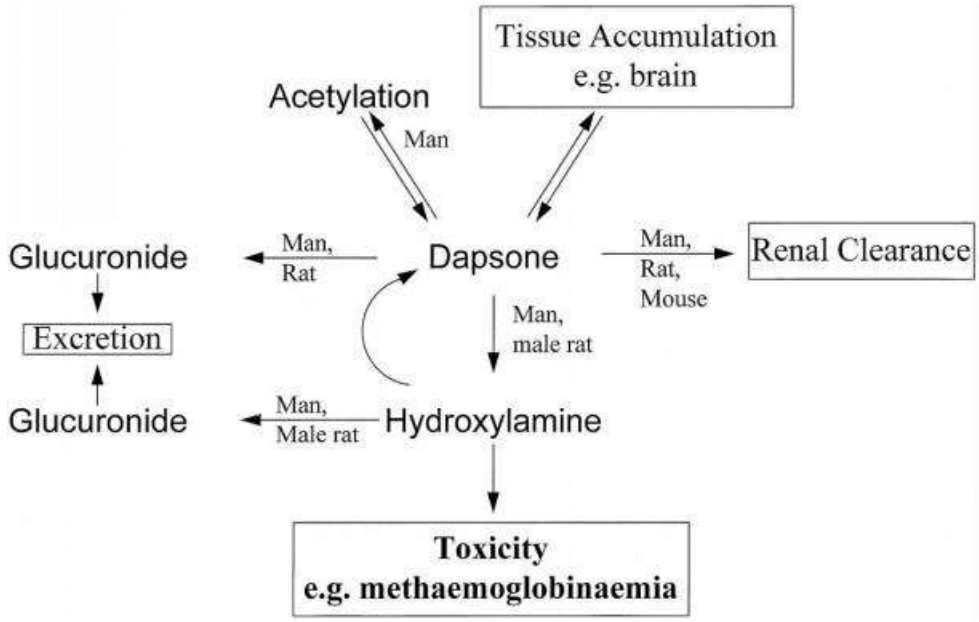


Figure 1. Antimicrobial mechanism of dapsone. DDS: 4,4'-diamino-diphenylsulfone; pABA: *p*-aminobenzoic acid; H2PtPP: 6-hydroxymethyl-7,8-dihydropterin-pyrophosphate; DHPS: 6-hydroxymethyl-7,8-dihydropteroate synthase.

OVERDOSE OF DAPSONE:

Manifestations of acute dapsone intoxication include vomiting, cyanosis, tachypnea, tachycardia, altered or depressed mental status, and seizures. Methemoglobinemia and sulf haemoglobinemia usually are observe within a few hours of the overdose, but intravascular haemolysis may be delayed. The illness lasts several days.



CONTRAINDICATIONS:

Dapsone is widely used in the treatment of leprosy and several chronic inflammatory dermatological conditions. Hypersensitivity reactions to dapsone are potentially fatal adverse drug reactions with unknown prevalence and risk factors. We performed a systematic review covering all reported cases of hypersensitivity reactions, in order to systematically summarize the published evidence on prevalence, clinical course and fatality rate. Articles were identified through standardized search strategies. Included studies were reviewed for hypersensitivity characteristics and odds ratios were calculated in univariate and multivariate regression models to assess the risk factors for fatal outcome. A total of 114 articles (17 epidemiological studies, 97 case reports) totalling 336 patients with hypersensitivity reactions were included for analysis. From the epidemiological studies a total hypersensitivity reaction prevalence rate of 1.4% (95% confidence interval 1.2–1.7%) was determined. Mucosal involvement, after hepatitis higher age and disease occurrence in non-affluent countries were associated .

METHODOLOGY

❖ **Study site:**

Study was carried out at Sai Sudha hospital, Kakinada .

❖ **Sample Duration:**

Study was conducted for a duration of six months.

❖ **Sample Size:** 50 patients each taking **TAB METHOTREXTATE** and **TAB DAPSONE**

❖ **Study design:** A prospective observational study.

❖ **Inclusion criteria** ○ All patients in dermatology OPD prescribed with either **TAB METHOTREXATE /TAB DAPSONE**.

○ Patients with baseline HB of >12g/dl

○ Patients of either sex, aged between 20-70 years

○ Patient willing to give consent .

❖ **Exclusion criteria:** ○ Patients with pregnancy and lactation ○ Patients below 20 years and above 70 yrs. ○ Patients who are already taking drugs that alters hematological profile ○ Patients with baseline HB of < 12g/ dl

❖ **Study duration:** study was be conducted for a period of six months.

❖ **Data collection:**

○ Data of hematological profiles of patients taking **TAB METHOTREXATE / TAB DAPSONE** was collected in patient proforma and assessed

○ Patient demographics like age, gender, past medical history, diagnosis was collected in a specially designed data collection form. ○ Lab parameters such as hematological profile was collected at baseline, after 2 weeks, after 4 weeks, after 2 months

❖ **Limitations:**

- ○ The survey does not take into consideration of the drugs other than methotrexate and dapsone
- ○ This survey does not include pregnant women ○ This study doesn't include lactating mothers

❖ **Uses:**

- ○ Identifying the key- evidence based prognostic factors in order to improve outcomes of patients prescribed with methotrexate and dapsone
- ○ Estimating the burden of comorbidities and diseased symptoms on patients receiving methotrexate therapy and dapsone therapy.

- Researching the effectiveness of drugs used in therapy
- Monitoring and comparing the adverse effects noticed among different patients.
- Monitoring and identifying drug related effects and their management.
- Helping for precise management of patients with adverse effects.

❖ **Statistical method used**

By using MS EXCEL, the Descriptive statistics such as frequency and percentage were calculated and bar graphs, pie charts were obtained.

Ethical committee clearance:

Institutional ethical committee approved our study. This was an observational study. It didn't involve any administration of drugs to humans or animals and as there is no collection of specimen or serum samples, informed consent form was collected from the patients to collect the data.

RESULTS

➢ **Table1: Gender wise distribution of patients in MTX Therapy**

This data showed that both male and female population were almost equally prescribed with MTX treatment . Out of 50 patients 26 (51.4 %) were male and 24 (48.6 %) were females.

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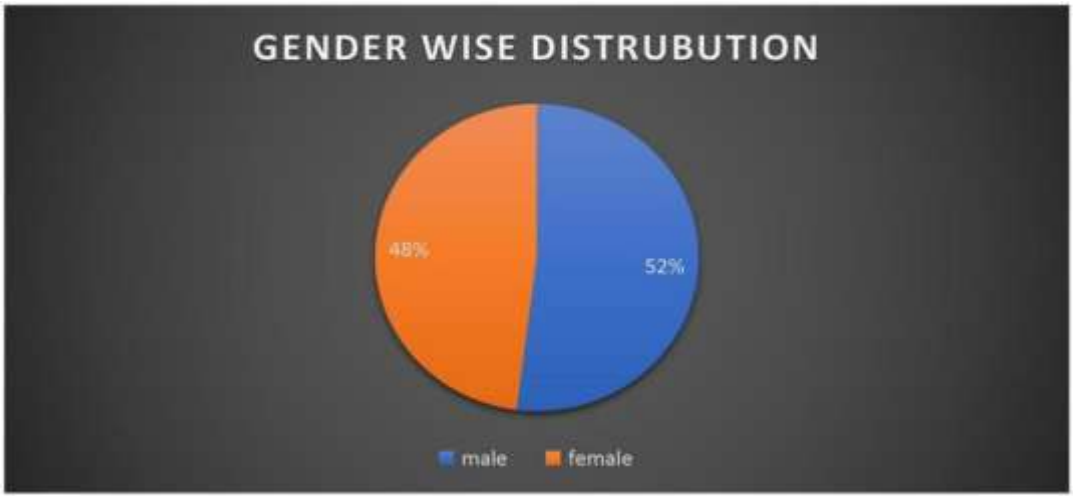
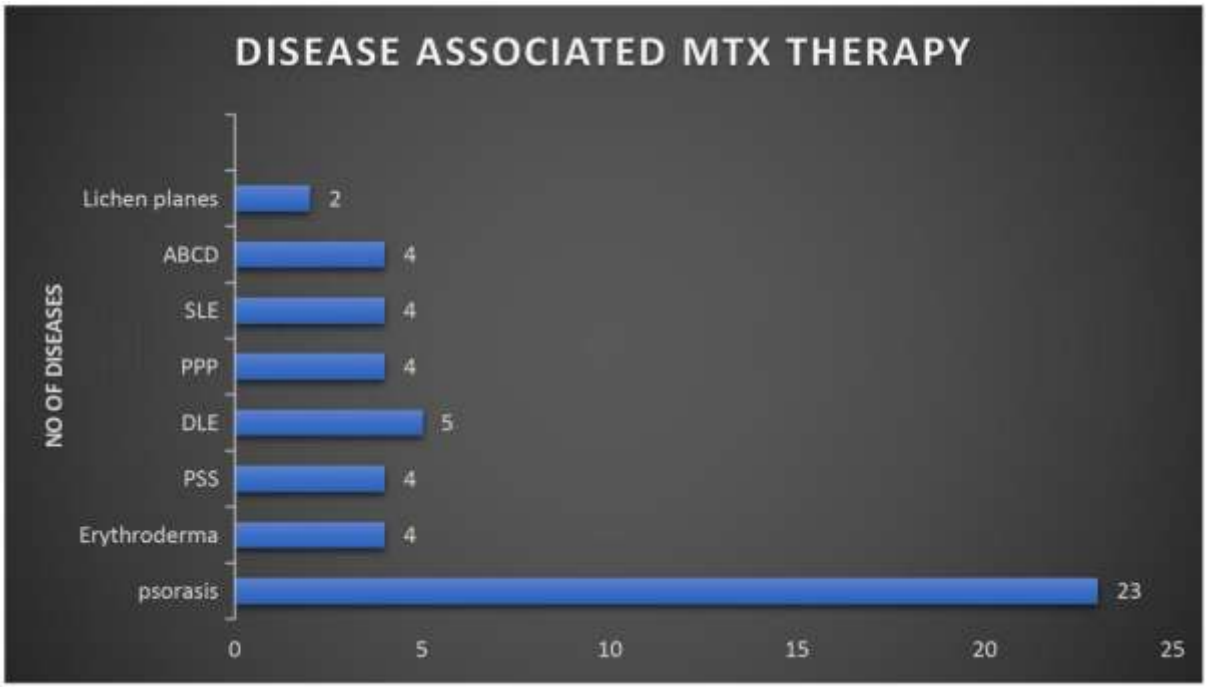
Gender	No. of Patients	Percentage
Male	26	51.4%
Female	24	48.6%
Total	50	100%



➢ **Table2: Representation of diagnosis associated in MTX therapy**

In a study population of 50 patients Majority of cases that were associated with methotrexate drug usage were psoriasis (46.0 %), exfoliative erythroderma (8.0%),progressive systematic sclerosis(pss) (8.0 %), , discoid lupus erythematous (DLE) (10.0 %), Plamo - planter psoriasis (ppp) (8.0%), systemic lupus erythroderma (8.0%), air borne contact dermatitis(ABCD) (8.0%), lichen planus (4,%),

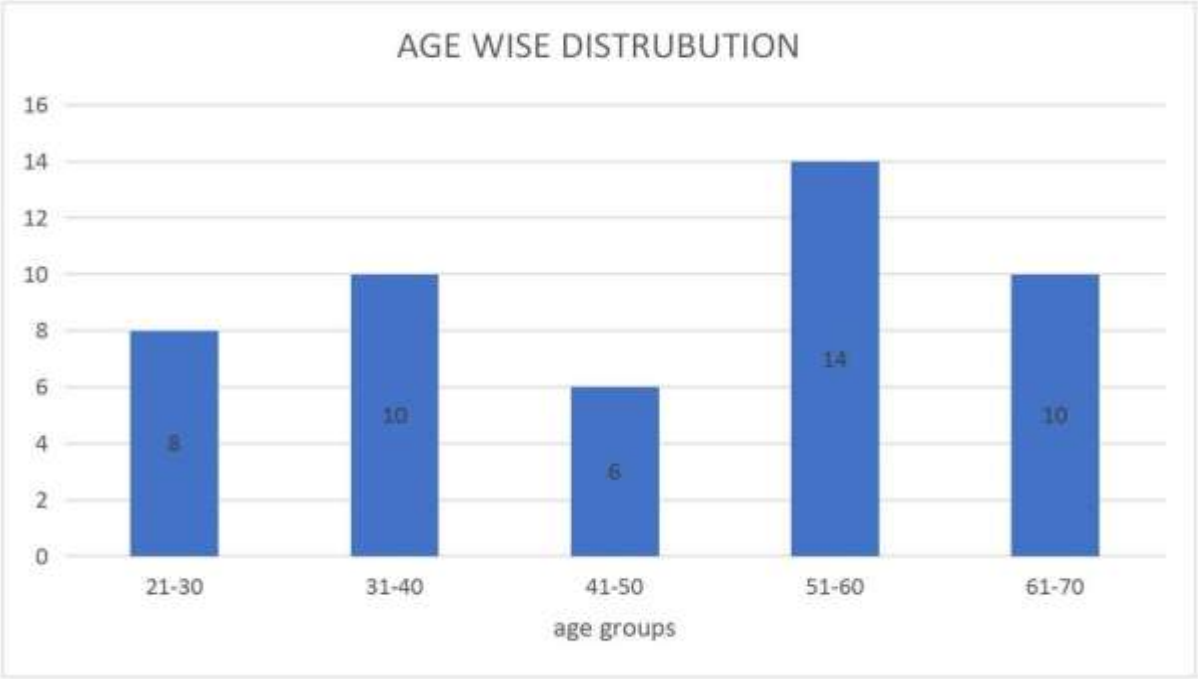
CONDITIONS	NO. OF CASES	PERCENTAGE
PSORIASIS	23	46.0%
ERYTHRODERMA	04	8.0%
PROGRESSIVE SYSTEMATIC SCLEROSIS(PSS)	04	8.0%
DISCOID LUPUS ERYTHREMATOUS(DLE)	05	10.0%
PALMO-PLANTER PSORASIS (PPP)	04	8.0%
SYSTEMIC LUPUS ERYTHRODERMA (SLE)	04	8.0%
AIR – BORNE CONTACT DERMATATIS (ABCD)	04	8.0%
LICHEN PLANEUS	02	4.0%
Total	50	100 %



➢ **Table 3: Age wise distribution in patients in MTX therapy**

Majority of patients belonged to age group 51- 60 years (32 %),followed by 61- 70 years (20 %), 31 – 40 years (20 %) , 21 – 30 years (16 %), 41- 50 years (12 %).

AGE	NO OF PATIENTS	PERCENTAGE
21 – 30 YEARS	08	16 %
31- 40 YEARS	10	20 %
41- 50 YEARS	06	12%
51- 60 YEARS	16	32%
61- 70 YEARS	10	20 %
TOTAL	50	100 %

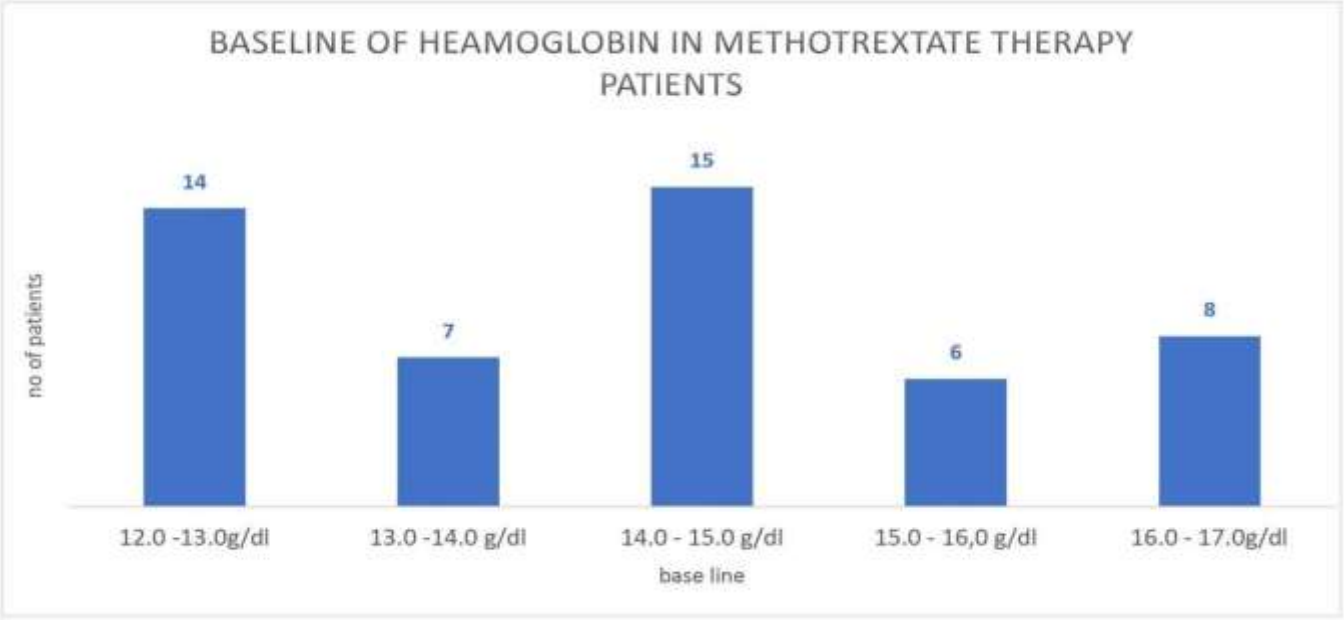


➢ **Table 4: Base line of haemoglobin in patients in MTX therapy**

Base line of haemoglobin in patients in MTX therapy

Out of 50 patients `14 patients had base line HB in range of (12.0 – 13.0 g/dl) , 4 patients had baseline HB in range of (13.0 – 14.0 g/dl), 10 patients had baseline HB in range of (14.0 – 15.0 g/dl) , 3 patients had baseline HB in range of (15.0 – 16.0 g/dl) , 5 patients had baseline HB in range of (16.0 – 17.0 g/dl).

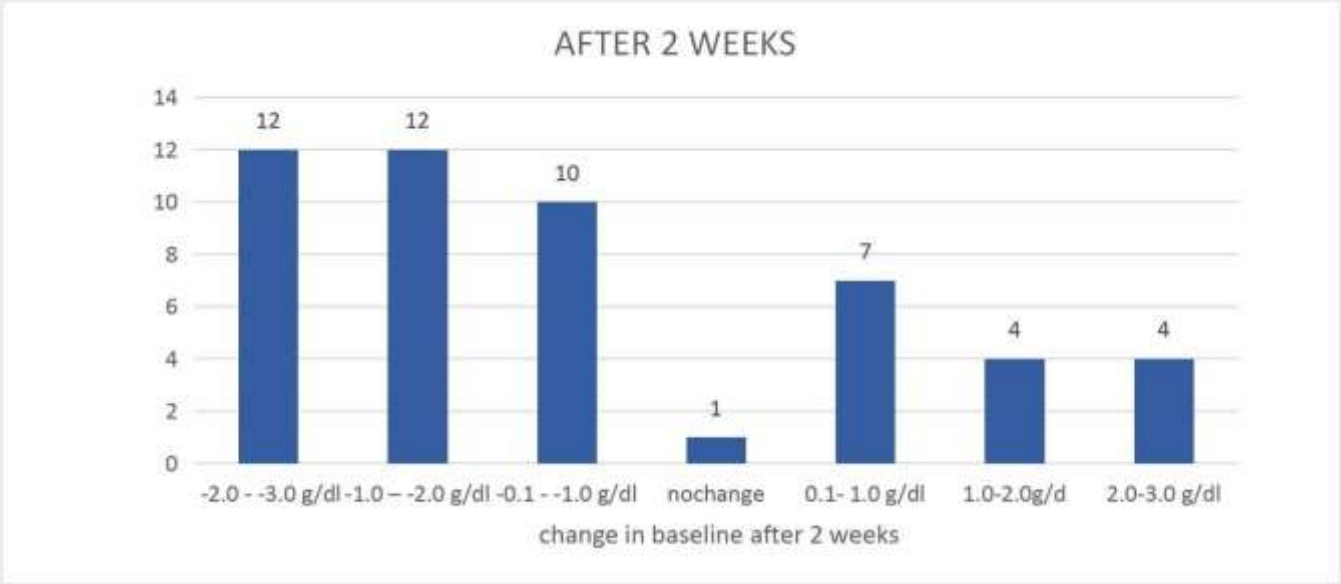
HAEMOGLOBIN	NO OF PATIENTS	PERCENTAGE
12.O – 13.0 g/dl	14	28 %
13.0 - 14.0 g/dl	07	14 %
14.0 – 15. g/dl	15	30 %
15.0 – 16.0 g/dl	06	12 %
16.0 – 17.0 g/dl	08	16 %
Total	50	100%



➢ **Table 5: Change in HB % (g/dl) from baseline after 2 weeks**

Out of 50 patients 1 patient had no change HB level at 2 weeks when compared to baseline , 34 patients had decrease in HB level with 12 patients showing decrease by 1- 2 gm %, 12 patients showing decrease by 2- 3 gm %, 10 patients showing less than 1 gm % decrease 15 patients had increase in haemoglobin level when compared to baseline , with 4 patients showing increase by 1-2 gm %,4 patients showing increase by 2 – 3 gm % , 7 patients showing up to 0.1 gm %.

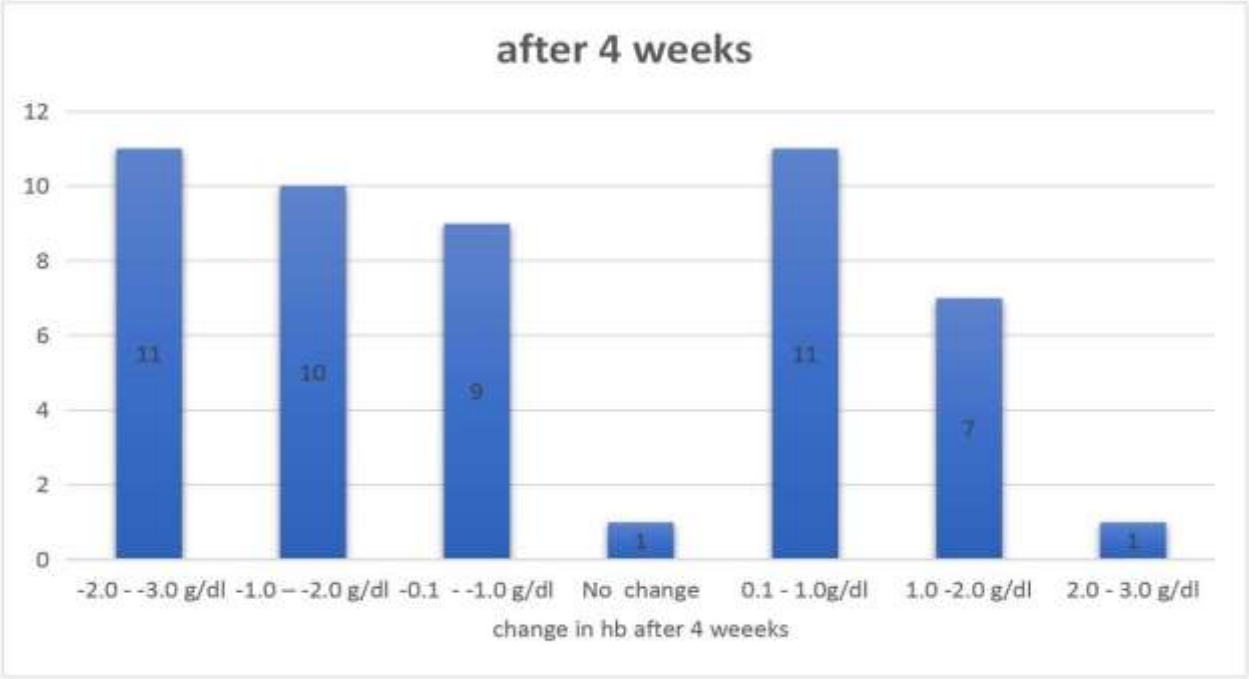
HB%	No of patients	Percentage
-2.0 - -3.0 g/dl	12	24 %
-1.0 – -2.0 g/dl	12	24%
-0.1 - -1.0 g/dl	10	20%
No change	01	02%
0.1– 1.0 g/dl	07	14%
1.0 – 2.0 g/dl	04	08%
2.0 – 3.0 g/dl	04	08%
Total	50	100%



➢ **Table 6: Changes in HB % (g/dl) from baseline after 4 weeks :**

Out of 50 patients 1 patient had no change HB level at 4 weeks when compared to baseline , 30 patients had decrease in HB level with 10 patients showing decrease by 1- 2 gm %, 11 patients showing decrease by 2- 3 gm %, 09 patients showing less than 1 gm % decrease 19 patients had increase in haemoglobin level when compared to baseline , with 7 patients showing increase by 1-2 gm %,1 patients showing increase by 2 – 3 gm % , 11 patients showing upto 1 gm %.

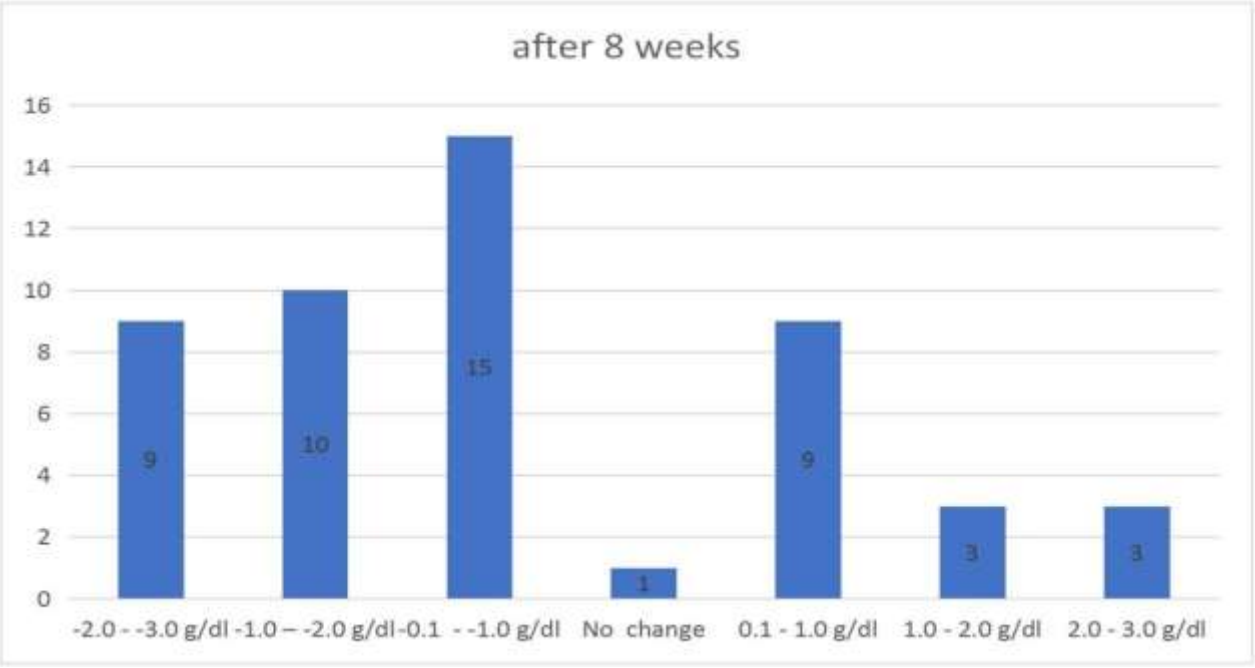
Change in baseline after 4 weeks	No of patients	Percentage
-2.0 - -3.0 g/dl	11	22%
-1.0 – -2.0 g/dl	10	20 %
-0.1 - -1.0 g/dl	09	18%
No change	01	02%
0.1– 1.0 g/dl	11	22%
1.0 – 2.0 g/dl	07	16 %
2.0 – 3.0 g/dl	.01	04%
Total	50	100%



➢ **Table 7: Change in HB % (g/dl) from baseline after 8 weeks :**

Out of 50 patients 1 patient had no change HB level at 2 months when compared to baseline , 34 patients had decrease in HB level with 10 patients showing decrease by 1- 2 gm %, 9 patients showing decrease by 2- 3 gm %, 09 patients showing less than 1 gm % decrease 15 patients had increase in haemoglobin level when compared to baseline , with 3 patients showing increase by 1-2 gm %,3 patients showing increase by 2 – 3 gm % , 9 patients showing up to 1 gm %.

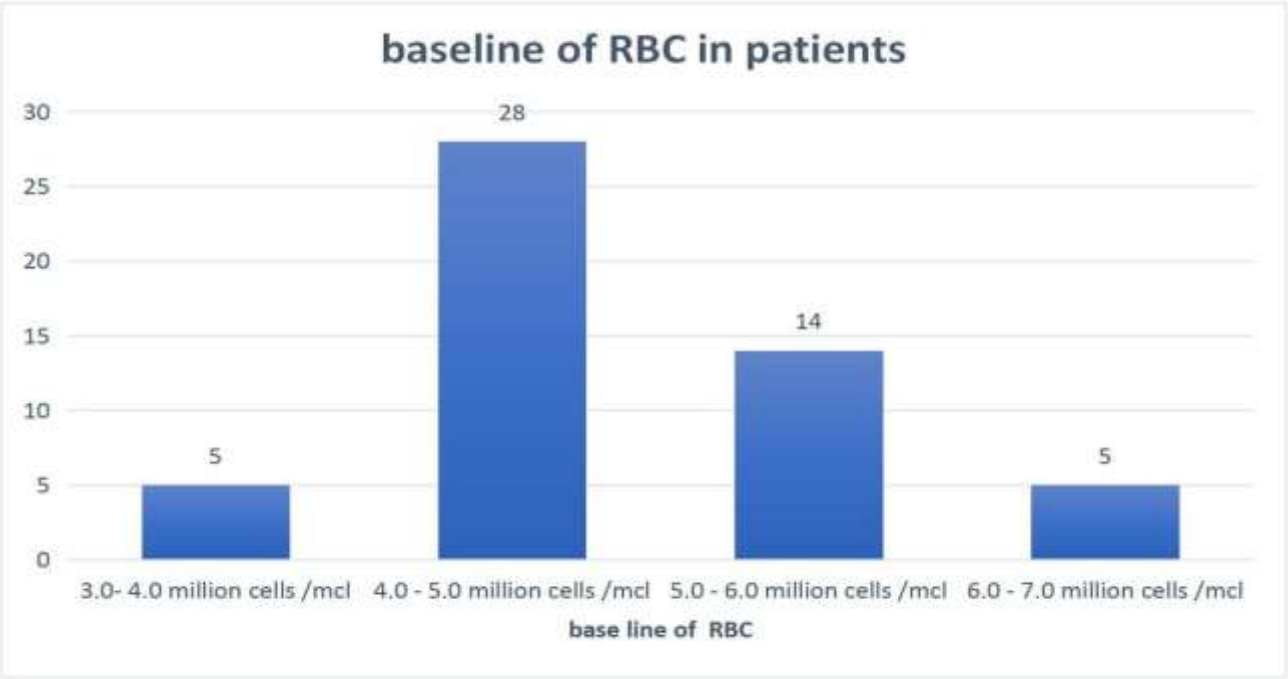
Hb %	no of patients	Percentage
-2.0 - -3.0 g/dl	09	18 %
-1.0 – -2.0 g/dl	10	20 %
-0.1 - -1.0 g/dl	15	30 %
No change	01	02 %
0.1– 1.0 g/dl	09	18 %
1.0 – 2.0 g/dl	03	06 %
2.0 – 3.0 g/dl	03	06 %
Total	50	100 %



➢ **Table 8: Base line of RBC level of patients in MTX therapy**

Out of 50 patients 5 had base line RBC in range of (3.0 – 4.0 million cells / mcl),28 patients had baseline RBC in range of (4.0- 5.0 million cells /mcl),14 patients had baseline RBC in range of(5.0- 6.0 million cells /mcl),3 patients had baseline of RBC in range of (6.0- 7.0 million cells /mcl)

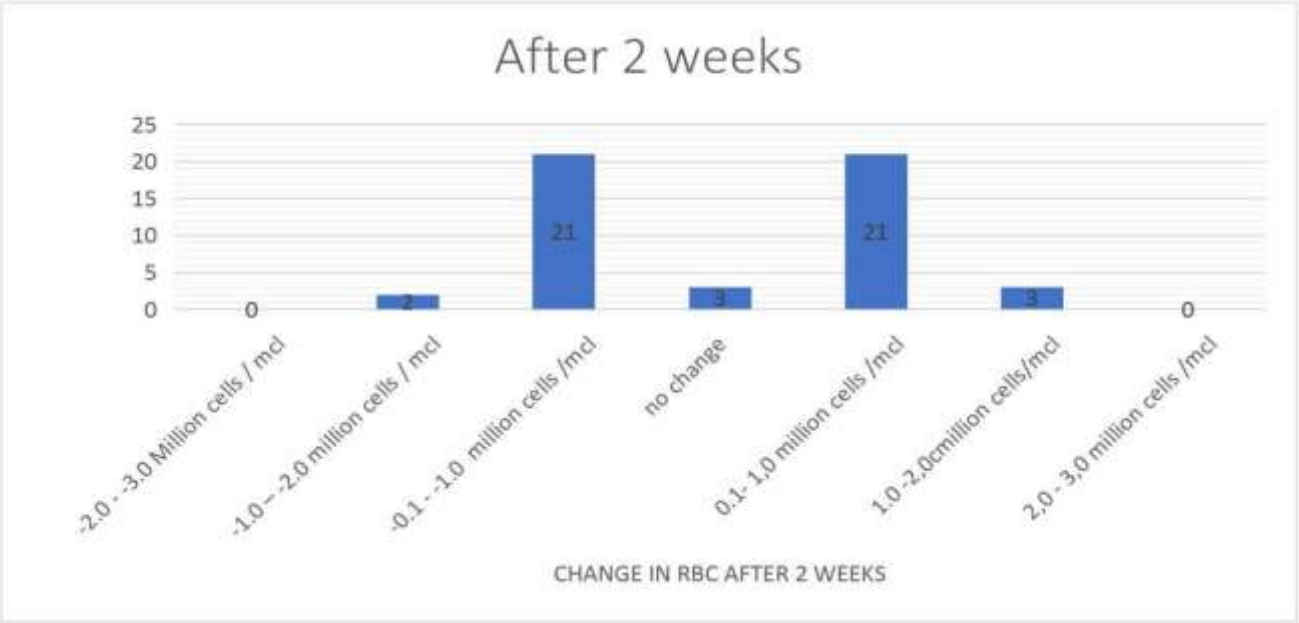
BASE LINE OF RBC	NO OF PATIENTS	Percentage
3.0 – 4.0 million cells/mcl	05	10 %
4.0 – 5.0 million cells /mcl	28	56 %
5.0 – 6.0 million cells /mcl	14	28 %
6.0 – 7.0 million cells /mcl	03	06 %
Total	50	100 %



➢ **Table 9: Changes in RBC from baseline after 2 weeks**

Out of 50 patients 3 patient had no change RBC level at 2 weeks when compared to baseline , 23 patients had decrease in RBC level with 2 patients showing decrease by 1- 2 gm %, 0 patients showing decrease by 2- 3 gm %, 21 patients showing less than 1 gm % decrease 24 patients had increase in haemoglobin level when compared to baseline , with 3 patients showing increase by 1-2 gm %, 0 patients showing increase by 2 – 3 gm % , 21 patients showing upto 1 gm %.

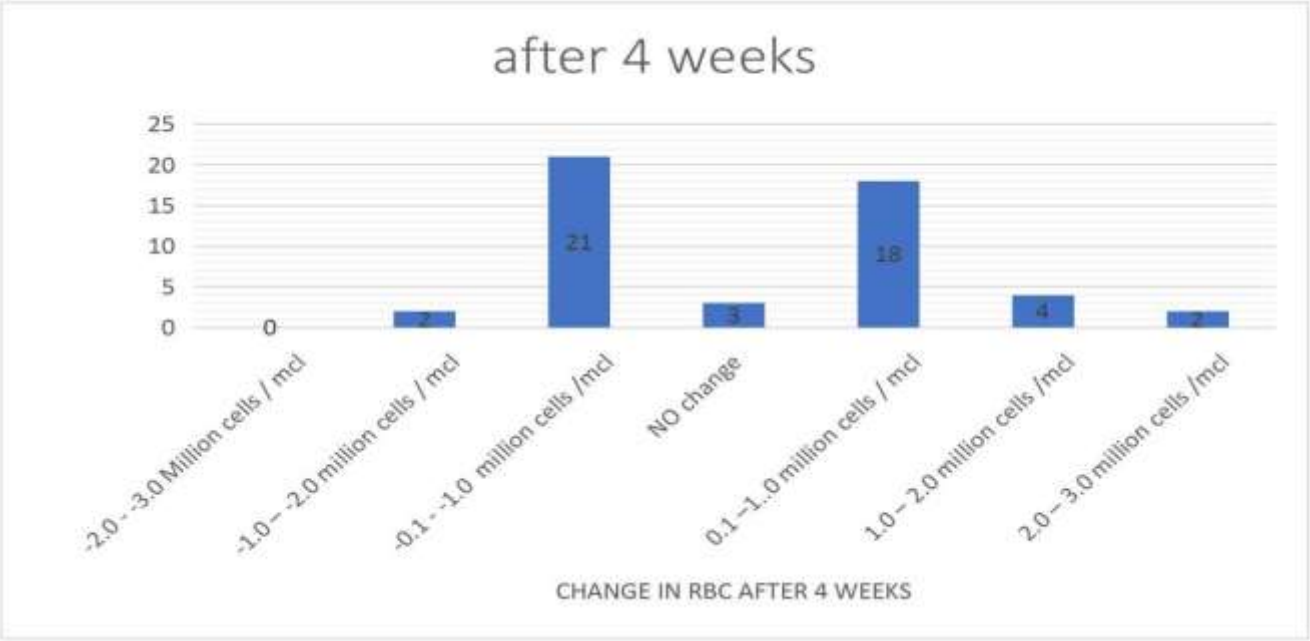
After two weeks of RBC	NO OF PATIENTS	Percentage
-2.0 - -3.0 Million cells / mcl	0	0 %
-1.0 – -2.0 million cells / mcl	2	4 %
-0.1 - -1.0 million cells /mcl	21	42%
NO change	3	06%
0.1 –1.0 million cells / mcl	21	42%
1.0 – 2.0 million cells /mcl	3	06%
2.0 – 3.0 million cells /mcl	0	0 %
Total	50	100%



➢ **Table10: Change in RBC from baseline after 4 weeks**

Out of 50 patients 3 patient had no change RBC level at 4 weeks when compared to baseline , 23 patients had decrease in RBC level with 2 patients showing decrease by 1- 2 gm %, 0 patients showing decrease by 2- 3 gm %, 21 patients showing less than 1 gm % decrease 24 patients had increase in haemoglobin level when compared to baseline , with 4 patients showing increase by 1-2 gm %, 2 patients showing increase by 2 – 3 gm % , 8 patients showing up to 1 gm %.

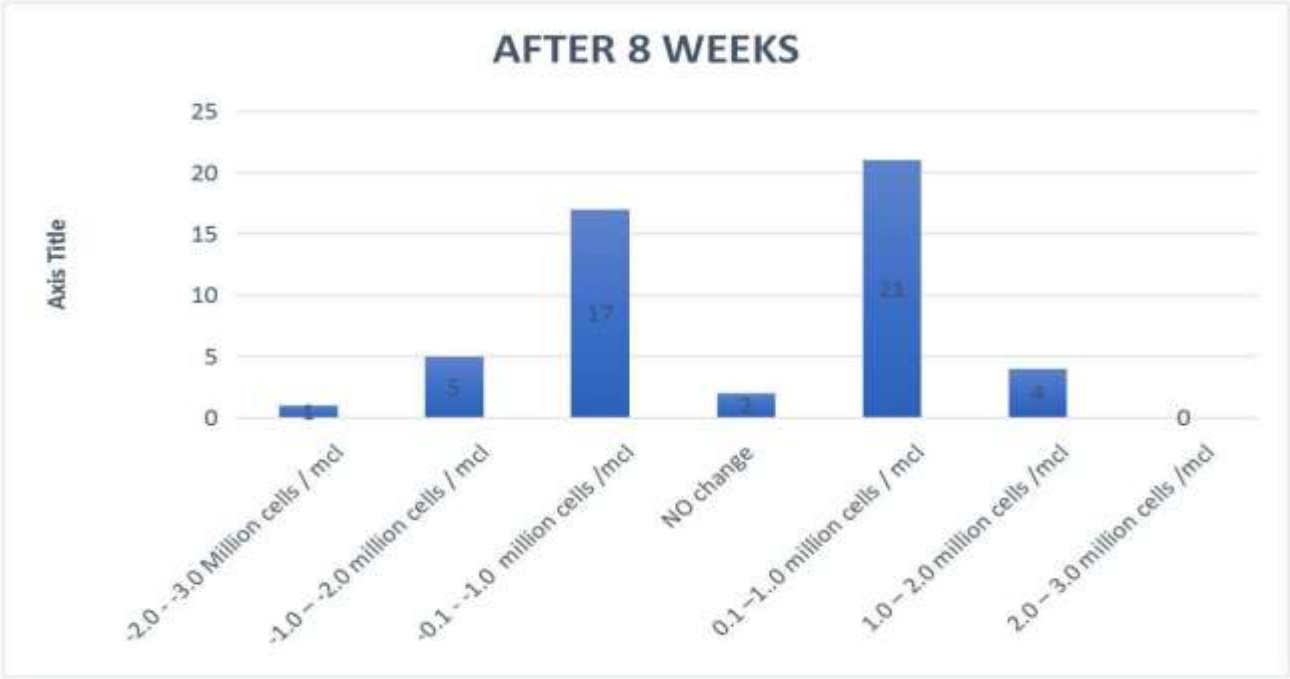
After four weeks of RBC	NO OF PATIENTS	Percentage
-2.0 - -3.0 Million cells / mcl	0	0 %
-1.0 – -2.0 million cells / mcl	2	4 %
-0.1 - -1.0 million cells /mcl	21	42%
NO change	3	06 %
0.1 –1.0 million cells / mcl	18	36%
1.0 – 2.0 million cel ls /mcl	4	08 %
2.0 – 3.0 million cells /mcl	2	04 %
Total	50	100%



➢ **Table 11: Changes in RBC from baseline after 8 weeks :**

Out of 50 patients 2 patient had no change RBC level at 2 months when compared to baseline , 23 patients had decrease in RBC level with 5 patients showing decrease by 1- 2 gm %, 1 patients showing decrease by 2-3 gm %, 17 patients showing less than 1 gm % decrease 25 patients had increase in haemoglobin level when compared to baseline , with 4 patients showing increase by 1-2 gm %, 0 patients showing increase by 2 – 3 gm % , 21 patients showing up to 1 gm %.

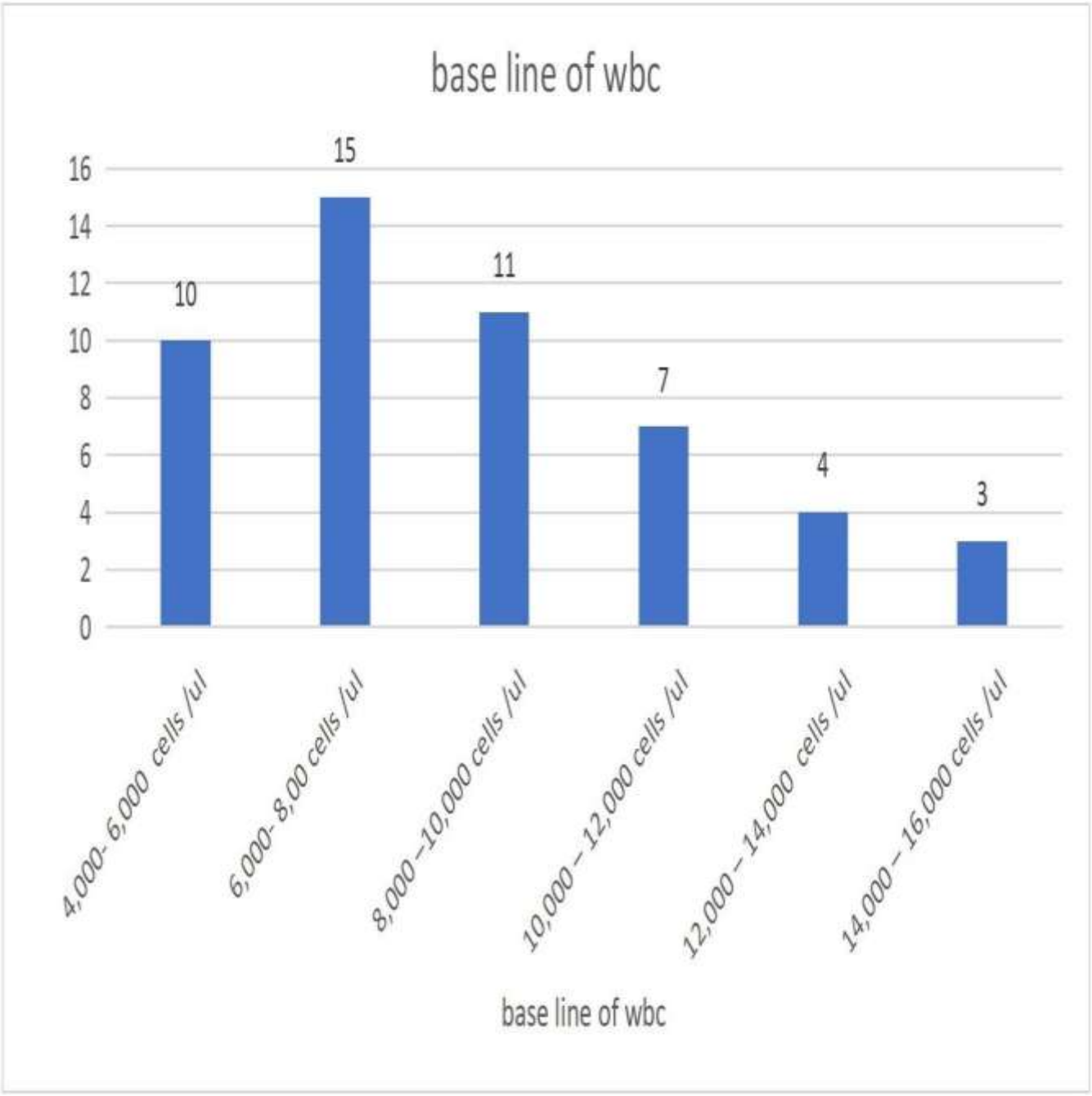
After two months of RBC	NO OF PATIENTS	PERCENTAGE
-2.0 - -3.0 Million cells / mcl	1	2 %
-1.0 – -2.0 million cells / mcl	5	10 %
-0.1 - -1.0 million cells /mcl	17	34%
NO change	2	4%
0.1 –1.0 million cells / mcl	21	42%
1.0 – 2.0 million cells /mcl	4	8 %
2.0 – 3.0 million cells /mcl	0	0 %
Total	50	100 %



➢ **Table 12: Base line of WBC in patients in MTX therapy**

Out of 50 patients 10 patients had baseline WBC in range of(4,000- 6,000 cells/ ul), 15 patients had baseline WBC in range of (6,000- 8,000 cells / ul), 11 patients had baseline WBC in range of (8,000- 10,000 cells /ul), 7 patients had baseline WBC in range of(10,00012,000 cells /ul), 4 patients had baseline WBC in range of (12,000- 14,000cells /ul), 3 patients had baseline WBC in range of (14,000- 16,000 cells /ul).

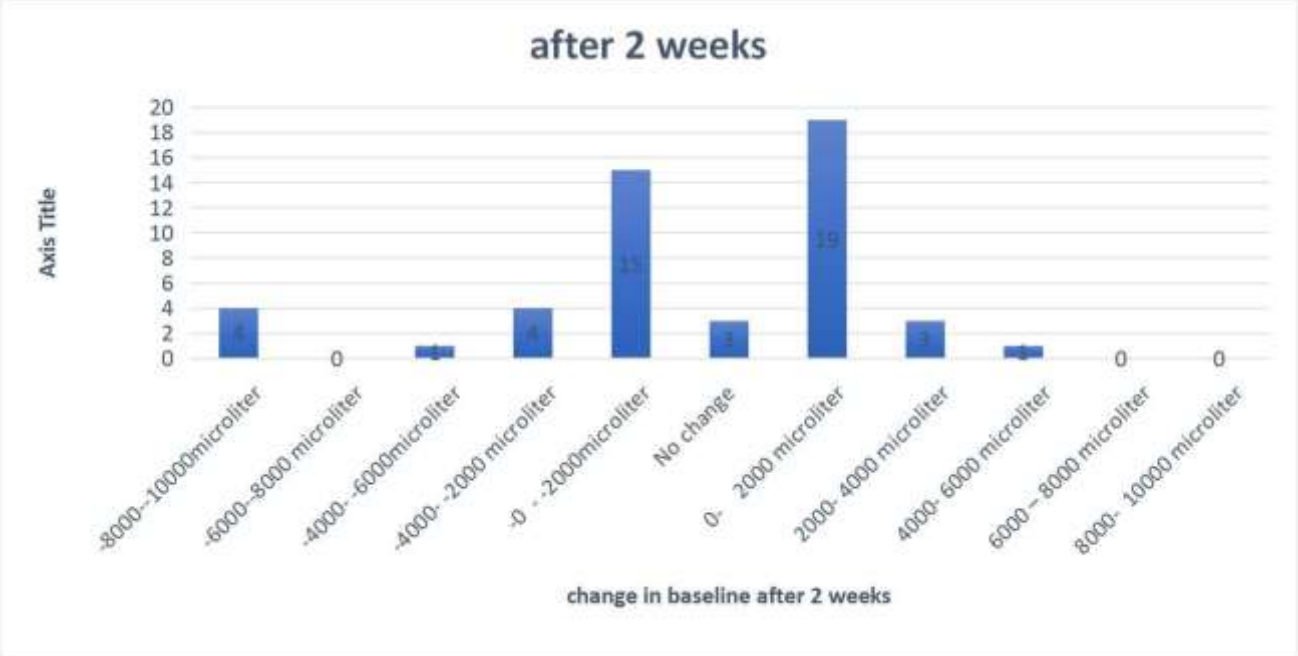
BASELINE OF WBC	NO OF PATIENTS	Percentage
4,000- 6,000 cells /ul	10	20 %
6,000- 8,000cells /ul	15	30 %
8,000 –10,000 cells /ul	11	22%
10,000 – 12,000 cells /ul	07	14 %
12,000 – 14,000 cells /ul	04	08%
14,000 – 16,000 cells /ul	03	06%
Total	50	100 %


base line of wbc
16
14
12
10
8
6
4
2
0
10
15
11
7
4
3
4,000- 6,000 cells /ul
6,000- 8,00 cells /ul
8,000 –10,000 cells /ul
10,000 – 12,000 cells /ul
12,000 – 14,000 cells /ul
14,000 – 16,000 cells /ul
base line of wbc

➢ **Table 13: Changes from baseline after 2 weeks**

Out of 50 patients 3 patient had no change WBC level at 2 months baseline , 22 patients had decrease in WBC level with 4 patients gm %, 4 patients showing decrease by 4-6 gm %, 1 patients showing gm %, 4 patients showing decrease by 8- 10 gm % ,15 patients showing 23 patients had increase in haemoglobin level when compared to baseline 3 showing increase by 2- 4 gm %,1 patients showing increase by 4-6 gm 1 showing increase by 6-8 gm %, 0 patients showing increase by 8- 10 gm %, 19 patients showing upto 1 gm %.

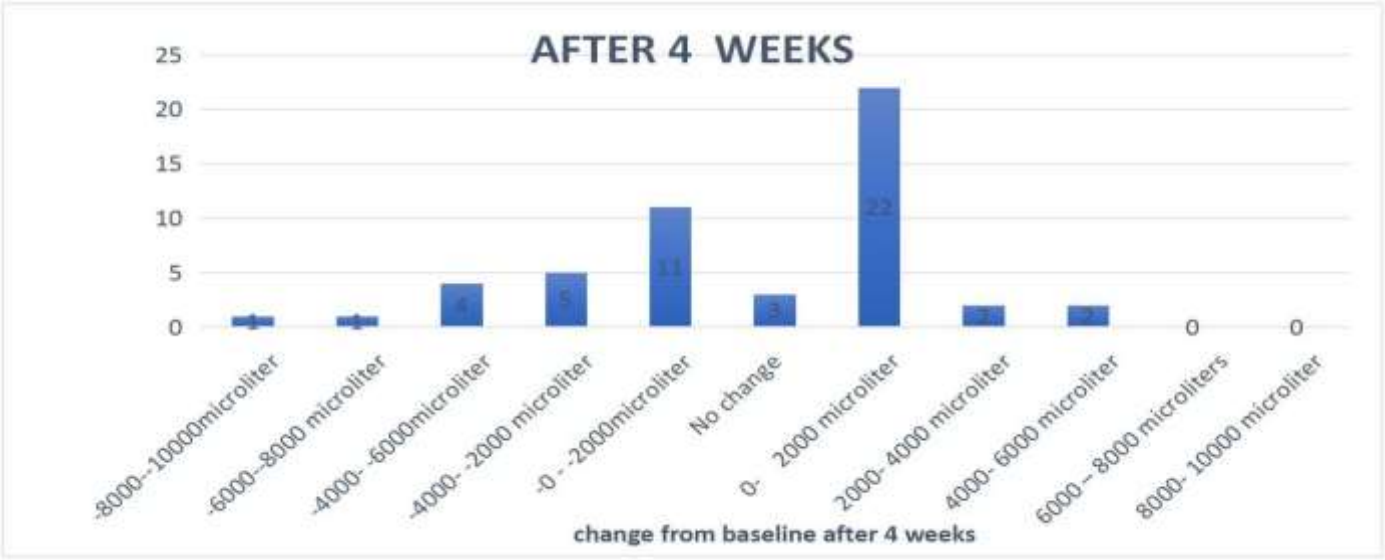
After 2 weeks	NO OF PATIENTS	Percentage
-8000—10000 microliter	04	08 %
-6000--8000 microliter	00	0 %
-4000- -6000microliter	01	2 %
-4000- -2000 microliter	04	08%
-0 - -2000microliter	15	30 %
No change	03	6%
0- 2000 microliter	19	38%
2000- 4000 microliter	03	06 %
4000- 6000 microliter	01	02 %
6000 – 8000 microliters	00	0%
8000- 10000 microliter	00	0%
Total	50	100 %



➢ **Table 14: Change from baseline after 4 weeks**

Out of 50 patients 3 patient had no change WBC level at 4weeks baseline , 22 patients had decrease in WBC level with 5 patients gm %, 4 patients showing decrease by 4-6 gm %, 1 patients showing gm %, 1 patients showing decrease by 8- 10 gm % ,15 patients showing 26 patients had increase in haemoglobin level when compared to baseline 2 showing increase by 2- 4 gm %, 2 patients showing increase by 4-6 gm 0 showing increase by 6-8 gm %, 0 patients showing increase by 8- 10 gm %, 22 patients showing upto 1 gm %

After 4 weeks	NO OF PATIENTS	Percentage
-8000--10000microliter	01	02 %
-6000--8000 microliter	01	02 %
-4000- -6000microliter	04	08%
-4000- -2000 microliter	05	10 %
-0 - -2000microliter	11	22%
No change	03	06%
0- 2000 microliter	22	44%
2000- 4000 microliter	02	04%
4000- 6000 microliter	02	04%
6000 – 8000 microliters	00	0 %
8000- 10000 microliter	00	0 %



Total	50	100 %

Table: 15: change from baseline after 8 weeks

Out of 50 patients 3 patient had no change WBC level at 8 weeks baseline , 31 patients had decrease in WBC level with 2 patients gm %, 3 patients showing decrease by 4-6 gm %, 0 patients showing gm %, 3 patients showing decrease by 8- 10 gm % ,23 patients showing 17 patients had increase in haemoglobin level when compared to baseline 2 showing increase by 2- 4 gm %, 0 patients showing increase by 4-6 gm 0 showing increase by 6-8 gm %, 0 patients showing increase by 8- 10 gm %, 15 patients showing up to 1 gm %

After 2 months	NO OF PATIENTS	PERCENTAGE
-8000--10000microliter	3	6 %
-6000--8000 microliter	0	0 %
-4000- -6000microliter	3	6 %
-4000- -2000 microliter	2	4 %
-0 - -2000microliter	23	46%
No change	2	4 %
0- 2000 microliter	15	30 %
2000- 4000 microliter	2	04 %
4000- 6000 microliter	0	0 %
6000 – 8000microliters	0	0 %
8000- 10000 microliter	0	0 %
Total	50	100%

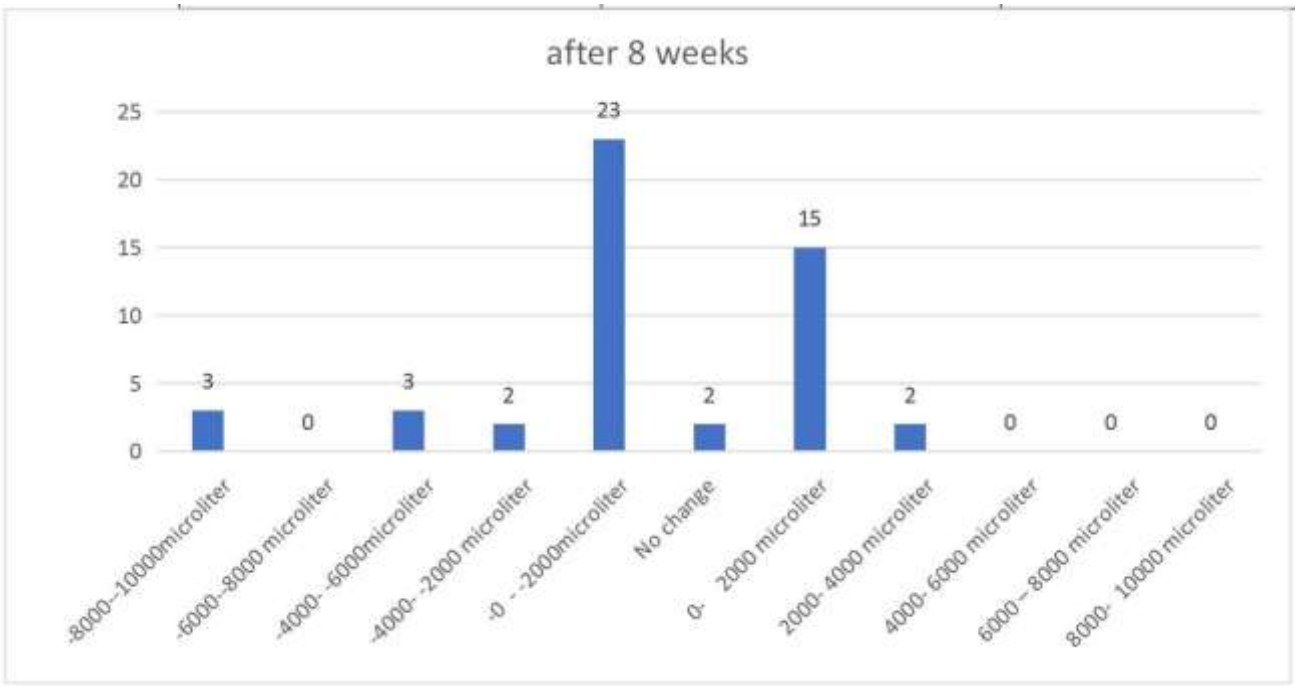
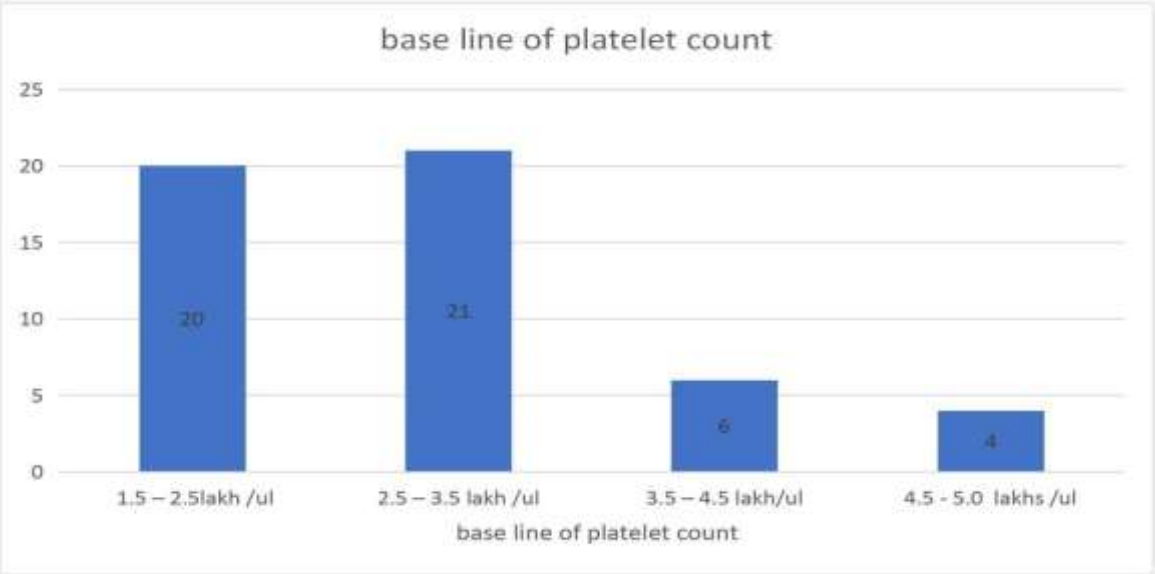


Table 16: Baseline of platelet count in patients in MTX therapy

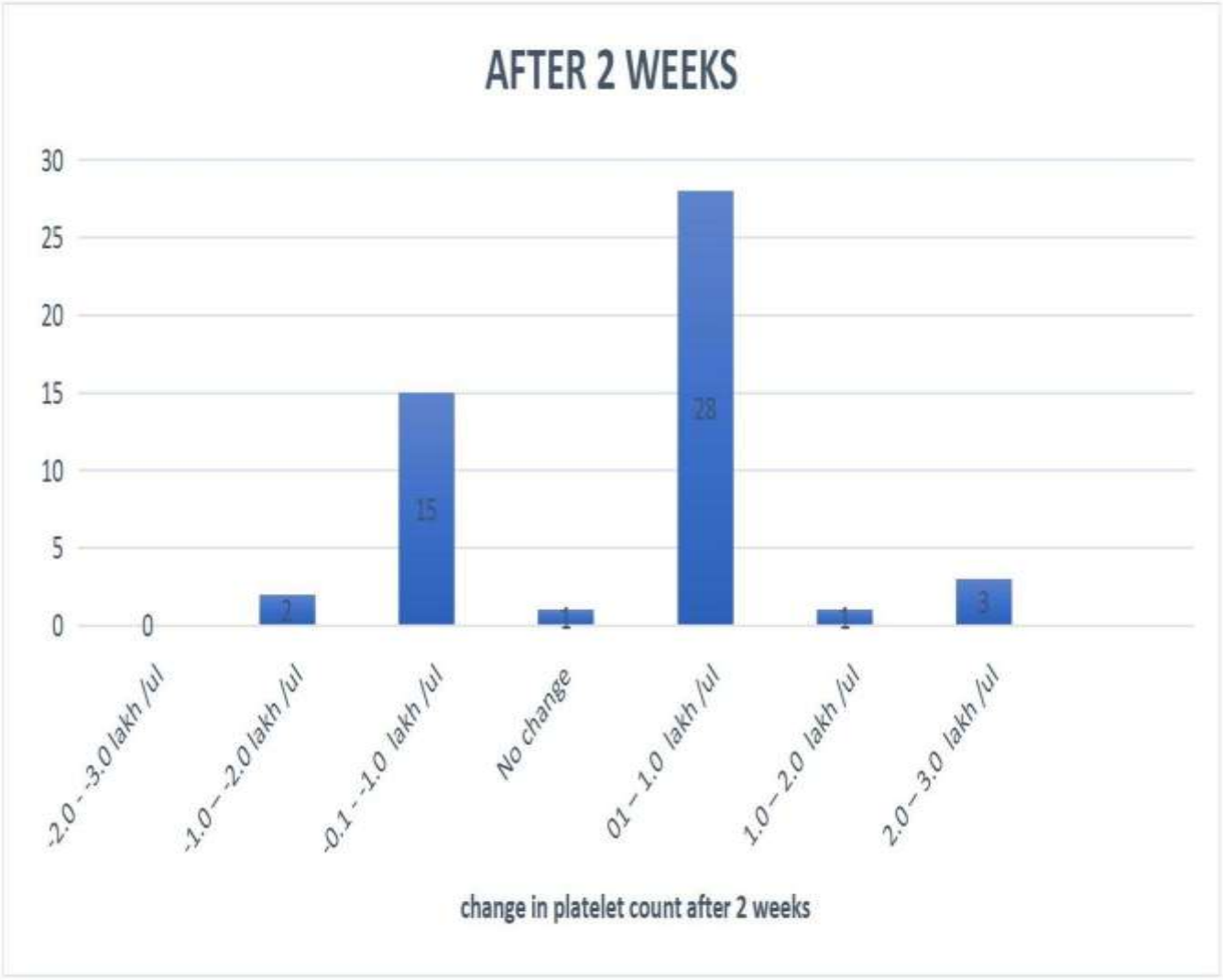
Out of 50 patients 20 patients had baseline platelet count in range of (1.5 – 2.5 lakh /ul) , 21 patients had baseline platelet count in range of (2.5 – 3.5lakh /ul), 06 patients had baseline platelet count in range of (3.5 – 4.5lakh /ul) , 4 patients had baseline platelet count in range of (4.5 – 5.0 lakh /ul).

Base line of platelet count	No of patients	Percentage
1.5 – 2.5lakh /ul	20	40 %
2.5 – 3.5 lakh /ul	20	40 %
3.5 – 4.5 lakh/ul	06	12 %
4.5 - 5.0 lakhs /ul	04	08 %
Total	50	100 %



After 2 weeks	No of patients	Percentage
-2.0 - -3.0 lakh /ul	00	0 %
-1.0 – -2.0 lakh /ul	02	4 %
-0.1 - -1.0 lakh /ul	15	30 %
No change	01	2 %
01 – 1.0 lakh /ul	28	46 %
1.0 – 2.0 lakh /ul	01	2 %
2.0 – 3.0 lakh /ul	03	6 %
Total	50	100 %

Table 17: Change of platelet count from baseline after 2 weeks Out of 50 patients 1 patients had no change platelet count at 2 weeks when compared to baseline , 17 patients had decrease in platelet count level with 2 patients showing decrease by 1- 2 gm %, 0 patients showing decrease by 2- 3 gm %, 15 patients showing less than 1 gm % decrease 32 patients had increase in haemoglobin level when compared to baseline , with 1 patients showing increase by 1-2 gm %, 3 patients showing increase by 2 – 3 gm % , 21 patients showing upto 1 gm %.



➢ **Table 18: Change in platelet count from baseline after 4 weeks**

Out of 50 patients 5 patients had no change platelet count at 4 weeks when compared to baseline , 19 patients had decrease in platelet count level with 0 patients showing decrease by 1- 2 gm %, 1 patients showing decrease by 2- 3 gm %, 18 patients showing less than 1 gm % , 26 patients had increase in haemoglobin level when compared to baseline , with 6 patients showing increase by 1-2 gm %, 1 patients showing increase by 2 – 3 gm % , 19 patients showing upto 1 gm %.

After 4 weeks	No of patients	Percentage
-2.0 - -3.0lakh /ul	01	02%
-1.0 – -2.0 lakh /ul	00	0%
-0.1 - -1.0 lakh /ul	18	36%
No change	05	10%
01 – 1.0 lakh /ul	19	38%
1.0 – 2.0 lakh /ul	06	32%
2.0 – 3.0 lakh /ul	01	02%
Total	50	100 %

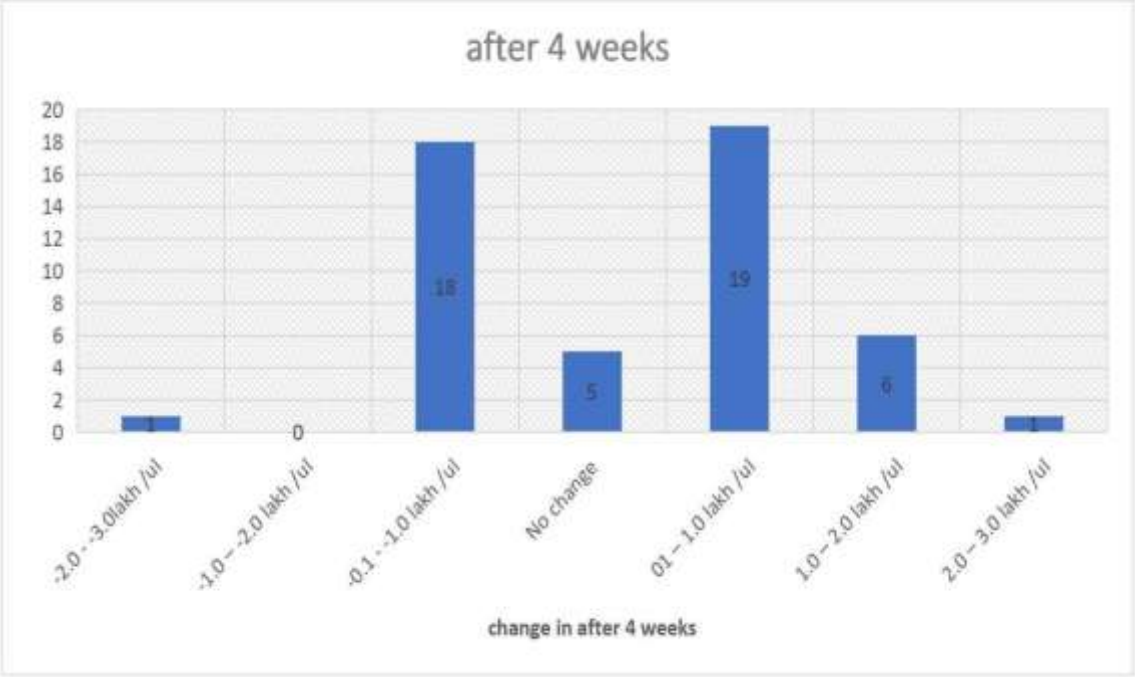


Table 19: Change in platelet count after 8 weeks

Out of 50 patients 1 patients had no change platelet count at 8 weeks when compared to baseline , 21 patients had decrease in platelet count level with 1 patients showing decrease by 1- 2 gm %, 0 patients showing decrease by 2- 3 gm %, 18 patients showing less than 1 gm % , 28 patients had increase in haemoglobin level when compared to baseline , with 3 patients showing increase by 1-2 gm %, 4 patients showing increase by 2 – 3 gm % , 21 patients showing upto 1 gm %.

After 2 months	No of patients	Percentage
-2.0 - -3.0 lakh / ul	00	0 %
-1.0 – -2.0 lakh /ul	03	6%
-0.1 - -1.0 lakh /ul	18	36%
No change	1	2%
01 – 1.0 lakh /ul	21	42%
1.0 – 2.0 lakh /ul	03	06%
2.0 – 3.0 lakh /ul	04	08%
Total	50	100 %

DAPSONE :

Table : 20 gender wise distribution of patients

This data showed that both male and female population were almost equally prescribed with dapsone treatment. 0ut of 50 patients 23 (46%) were male and 27 (54 %) were females.

Gender	No. of Patients	Percentage
Male	23	46%
Female	27	54%
Total	50	100%

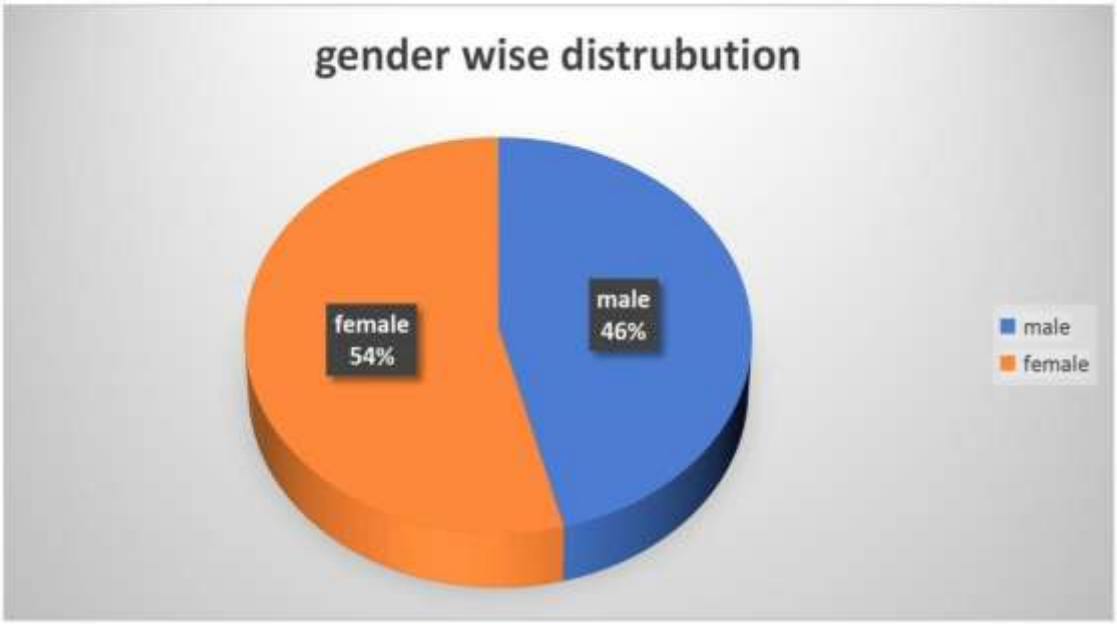


Table21: Representation of diagnosis associated in dapsone therapy

In a study population of 50 patient's majority of cases that were associated with dapsone drug usage were common in these diseases

CONDITIONS	NO. OF CASES	PERCENTAGE
Hansen's disease	5	10 %
Acne	10	20 %
Lichen planus	13	26%
LPP lichen planus pigmentosus)	04	08%
Bullous pemphigod	05	10 %
Tropic ulcer	05	10 %
BECHETS DISEASE	01	02 %
Chronic urticaria	02	04%
Pemphigus vulgaris	05	10%
Total	50	100 %

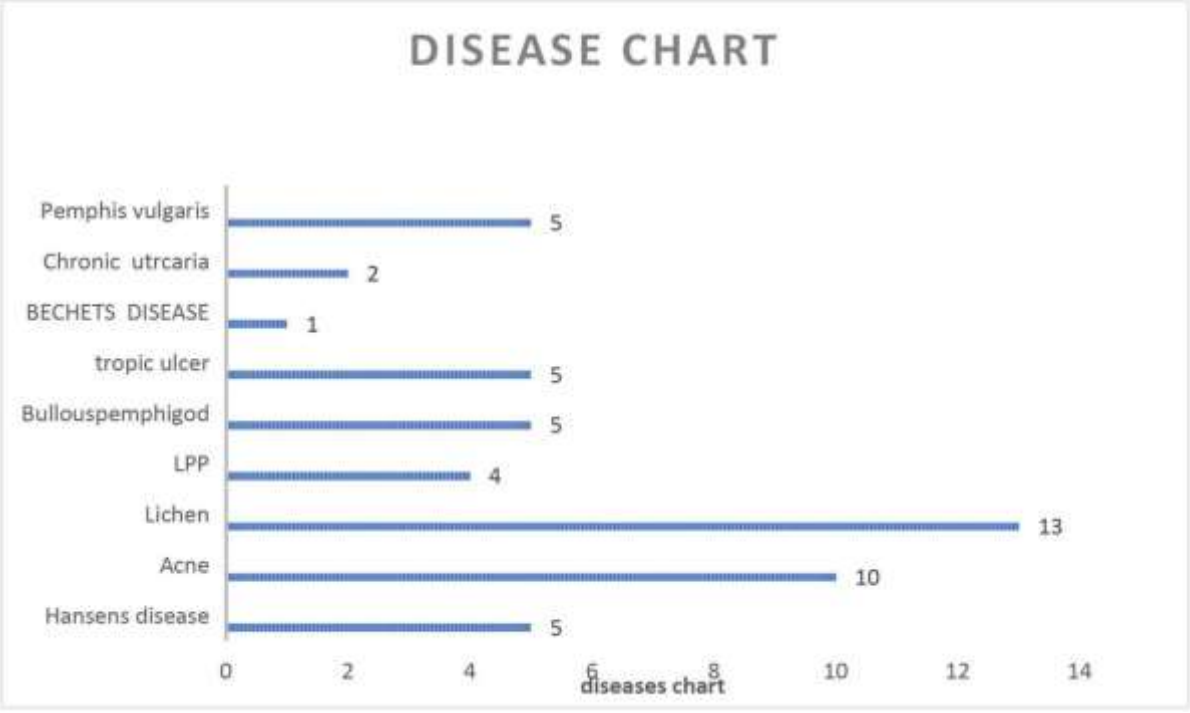


Table 22: Age wise distribution in patients in dapsone therapy

Majority of patients belonged to age group of 21 – 30 years (28%) followed by 61 – 70 years (18%), 51- 60 years (14 %), 41 – 50 years (11 %), 31 – 40 years (10%).

AGE GROUP	NO OF PATIENTS	PERCENTAGE
21 – 30 YEARS	14	28%
31- 40 YEARS	05	10%
41- 50 YEARS	11	22%
51- 60 YEARS	07	14%
61- 70 YEARS	09	18%
TOTAL	50	100 %

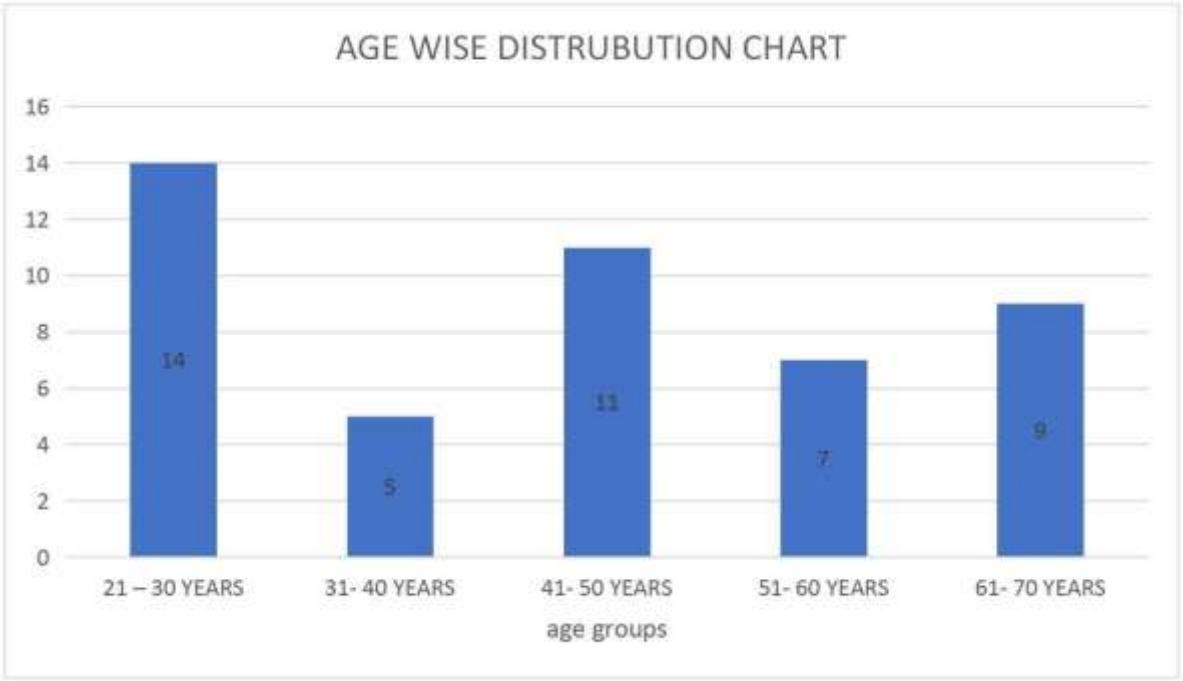


Table 23 : Base line of haemoglobin in patients in DAPSONE therapy

Base line of haemoglobin in patients in dapsone therapy

Out of 50 patients `18 patients had base line HB in range of (12.0 – 13.0 g/dl), 13 patients had baseline in range of (13.0 – 14.0 g/dl), 11 patients had baseline in range of (14.0 – 15.0 g/dl) , 6 patients had baseline in range of (15.0 – 16.0 g/dl) , 2 patients had baseline in range of (16.0 – 17.0 g/dl).

HAEMOGLOBIN	NO OF PATIENTS	Percentage
12.O – 13.0 g/dl	18	36%
13.0 - 14.0 g/dl	13	26%
14.0 – 15. g/dl	11	22%
15.0 – 16.0 g/dl	06	12%
16.0 – 17.0 g/dl	02	4%
Total	50	100%

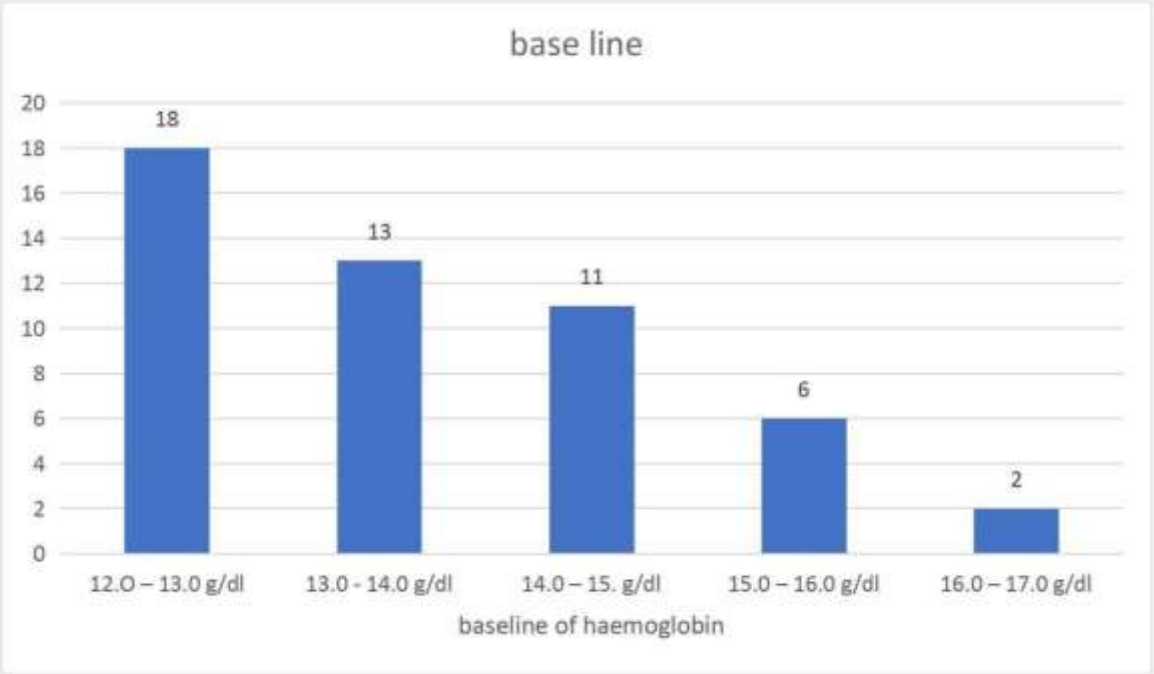


Table 24: Change in HB % (g/dl) from baseline after 2 weeks

Out of 50 patients 1 patient had no change HB level at 2 weeks when compared to baseline , 43 patients had decrease in HB level with 13 patients showing decrease by 1- 2 gm %, 04 patients showing decrease by 2- 3 gm %, 13 patients showing decrease by 3- 4 gm %,13 patients showing less than 1 gm % .06 patients had increase in haemoglobin level when compared to baseline , with 0 patients showing increase by 1-2 gm %,0 patients showing increase by 2 – 3 gm % , 0 patients showing more than 3- 4 gm %,6 patients showing upto than 0.1 gm%.

HB%	No of patients	Percentage
-3.0 – - 4.0 g/dl	13	26 %
-2.0 - -3.0 g/dl	04	8%
-1.0 – -2.0 g/dl	13	26%
-0.1 - -1.0 g/dl	13	26%
No change	01	2%
0.1– 1.0 g/dl	06	12%
1.0 – 2.0 g/dl	00	0 %
2.0 – 3.0 g/dl	00	0%
3.0 – 4.0 g/dl	00	0%
Total	50	100%

Table 25: Changes in HB % (g/dl) from baseline after 4 weeks

Out of 50 patients 1 patient had no change HB level at 4 weeks when compared to baseline , 43 patients had decrease in HB level with 13 patients showing decrease by 1- 2 gm %, 4 patients showing decrease by 2- 3 gm %, 13patients showing decrease by 3-4 gm %13 patients showing less than 1 gm % 6 patients had increase in haemoglobin level when compared to baseline , with 0 patients showing increase by 1-2 gm %,0 patients showing increase by 2 – 3 gm % , 0 patients showing increase by 3-4 gm % 6 patients showing upto than 0.1 gm %

Change after 4 weeks	No of patients	Percentage
-3.0 - - 4.0 g/dl	13	26%
-2.0 - -3.0 g/dl	04	08 %
-1.0 – -2.0 g/dl	13	26 %
-0.1 - -1.0 g/dl	13	26%
No change	01	2%
0.1– 1.0 g/dl	06	12%
1.0 – 2.0 g/dl	00	0%
2.0 – 3.0 g/dl	00	0%
3.0 – 4.0 g/dl	00	0%
Total	50	10

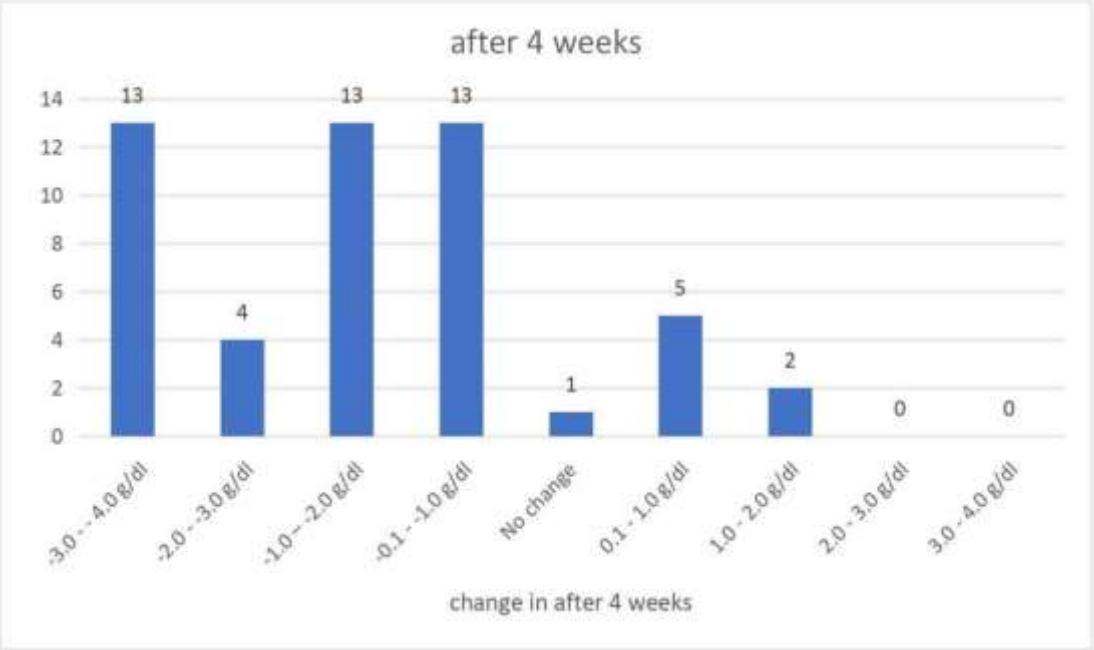


Table 26: Change in HB % (g/dl) from baseline after 8 weeks

Out of 50 patients 1 patient had no change HB level at 8 weeks when compared to baseline , 42 patients had decrease in HB level with 13 patients showing decrease by 1- 2 gm %, 5 patients showing decrease by 2- 3 gm %, 20 patients showing decrease by 3-4 gm %4 patients showing less than 1 gm % 7 patients had increase in haemoglobin level when compared to baseline , with 2 patients showing increase by 1-2 gm %,0 patients showing increase by 2 – 3 gm % , 0 patients showing increase by 3-4 gm % 5 patients showing upto than 0.1 gm %

Hb %	no of patients	Percentage
-3.0- 4.0 g/dl	20	40%
-2.0 - -3.0 g/dl	05	10%
-1.0 – -2.0 g/dl	13	26%
-0.1 - -1.0 g/dl	04	08%
No change	01	2%
0.1– 1.0 g/dl	05	10%
1.0 – 2.0 g/dl	02	4%
2.0 – 3.0 g/dl	00	0%
3.0 – 4.0 g/dl	00	0%
Total	50	100%

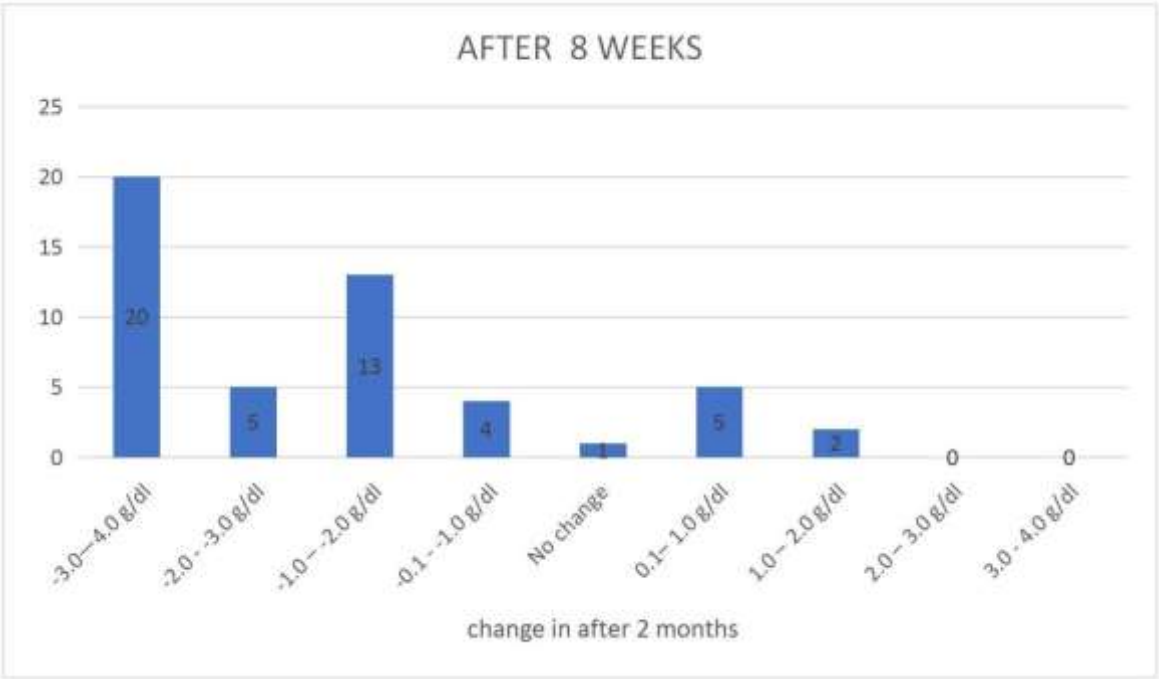


Table : 27 Baseline of RBC in dapsone therapy

Out of 50 patients 21 had base line RBC in range of (3.0 – 4.0 million cells / mcl),10 patients had baseline RBC in range of (4.0- 5.0 million cells /mcl),18 patients had baseline RBC in range of(5.0- 6.0 million cells /mcl),1patients had baseline of RBC in range of (6.07.0 million cells /mcl)

BASE LINE OF RBC	NO OF PATIENTS	Percentage
3.0 – 4.0 million cells/mcl	21	44%
4.0 – 5.0 million cells /mcl	10	20%
5.0 – 6.0 million cells /mcl	18	36%
6.0 – 7.0 million cells /mcl	01	02%
Total	50	100%

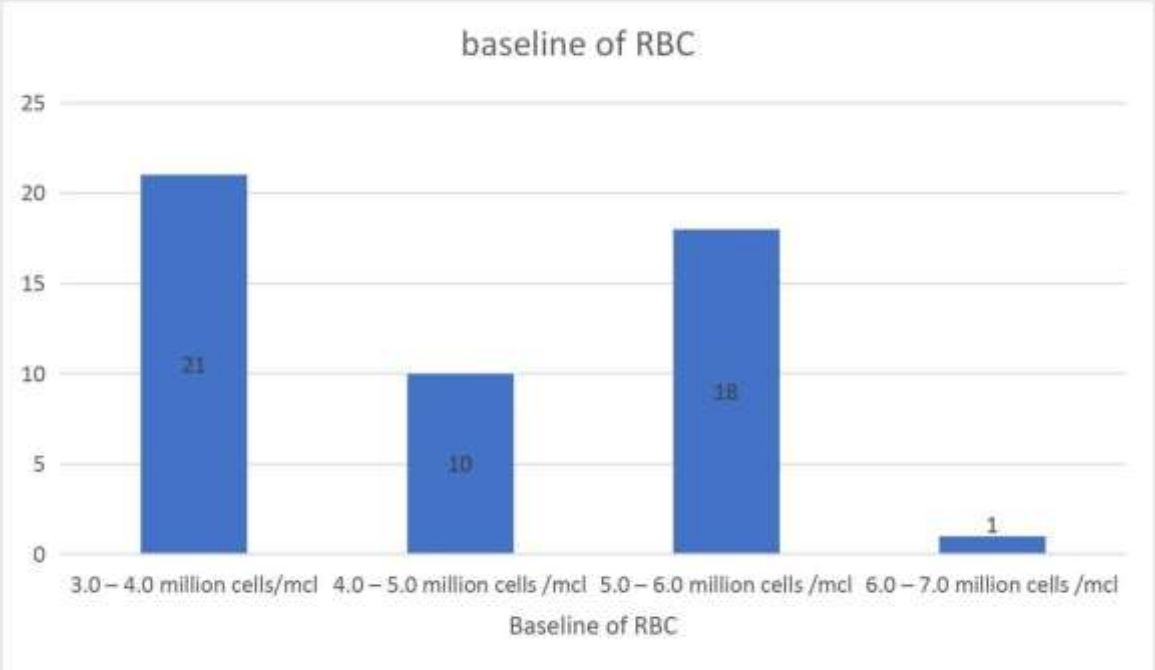
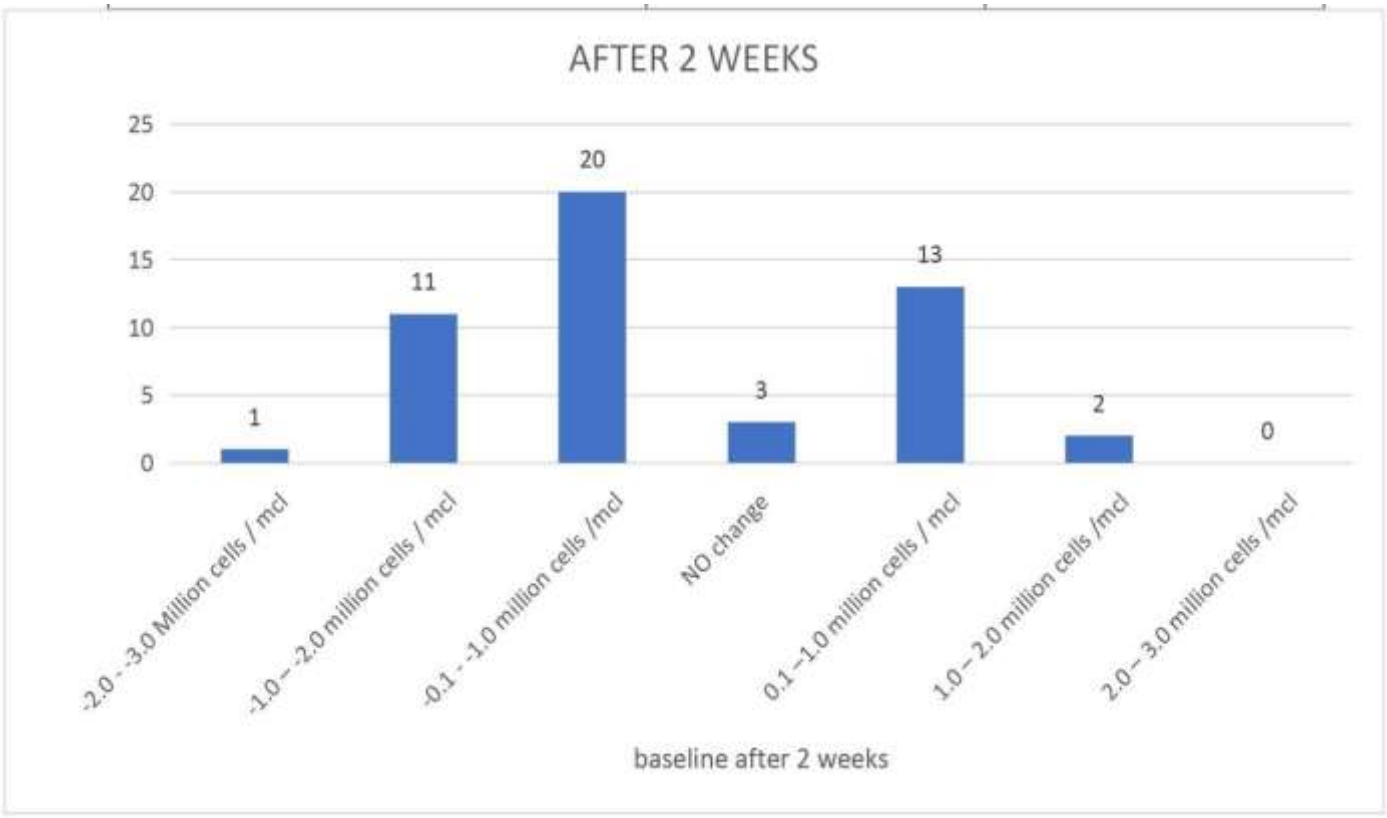


Table 28: Changes in RBC from baseline after 2 weeks

Out of 50 patients 3 patient had no change RBC level at 2 weeks baseline , 32 patients had decrease in RBC level with 11 patients showing decrease by 1- 2 gm %, 1 patients showing decrease by 2- 3 gm %, 20 patients showing less than 1 gm % 15 patients had increase in haemoglobin level when compared to baseline , with 2 patients showing increase by 1-2 gm %, 0 patients showing increase by 2 – 3 gm % , 13 patients showing upto 1 gm %.

After two weeks of RBC	NO OF PATIENTS	Percentage
-2.0 - -3.0 Million cells / mcl	01	2 %
-1.0 – -2.0 million cells / mcl	11	22%
-0.1 - -1.0 million cells /mcl	20	40%
NO change	03	06%
0.1 –1.0 million cells / mcl	13	26%
1.0 – 2.0 million cells /mcl	02	4%
2.0 – 3.0 million cells /mcl	00	0%



Total	50	100%

Table 29 : Changes in RBC from baseline after 4 weeks

Out of 50 patients 3 patient had no change RBC level at 4 weeks baseline , 33 patients had decrease in RBC level with 11 patients showing decrease by 1- 2 gm %, 5 patients showing decrease by 2- 3 gm %, 17 patients showing less than 1 gm % 13 patients had increase in haemoglobin level when compared to baseline , with 2 patients showing increase by 1-2 gm %, 0 patients showing increase by 2 – 3 gm % , 11
patients showing upto 1 gm %.

After 4 weeks of RBC	NO OF PATIENTS	Percentage
-2.0 - -3.0 Million cells / mcl	05	10 %
-1.0 – -2.0 million cells / mcl	11	22%
-0.1 - -1.0 million cells /mcl	17	34%
NO change	03	06%
0.1 –1.0 million cells / mcl	11	22%
1.0 – 2.0 million cells /mcl	02	4%
2.0 – 3.0 million cells /mcl	0	0 %
Total	50	100%

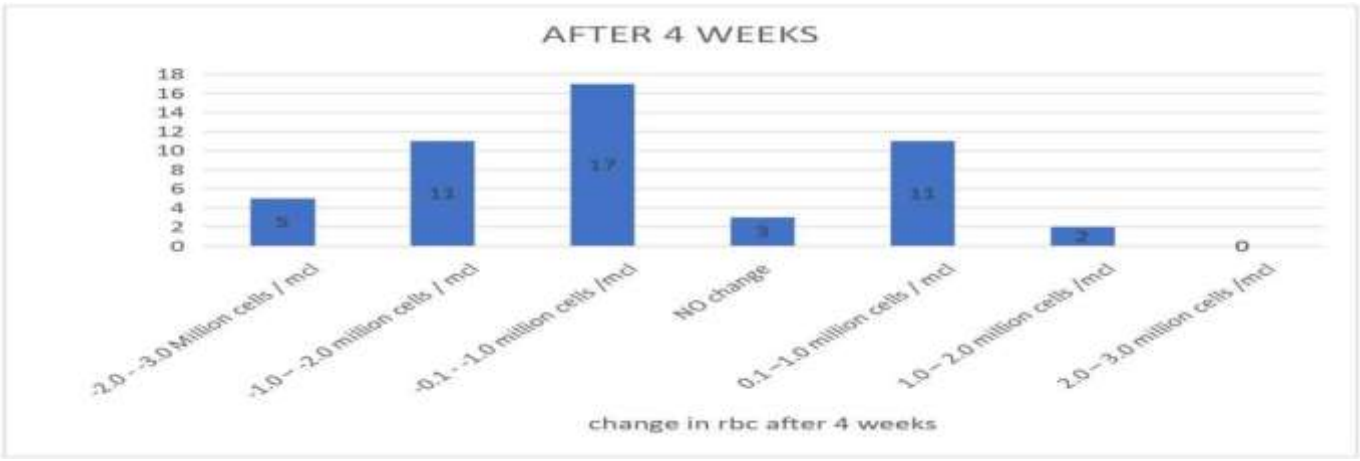


Table 30: Changes in RBC from baseline after 8 weeks

Out of 50 patients 5 patient had no change RBC level at 8 weeks baseline , 36 patients had decrease in RBC level with 10 patients showing decrease by 1- 2 gm %, 4 patients showing decrease by 2- 3 gm %, 22 patients showing less than 1 gm % 09 patients had increase in haemoglobin level when compared to baseline , with 2 patients showing increase by 1-2 gm %, 1 patients showing increase by 2 – 3 gm % , 6 patients showing upto 1 gm %.

After two months of RBC	NO OF PATIENTS	Percentage
-2.0 - -3.0 Million cells / mcl	04	08%
-1.0 – -2.0 million cells / mcl	10	20%
-0.1 - -1.0 million cells /mcl	22	44%
NO change	05	10%
0.1 –1.0 million cells / mcl	06	12%
1.0 – 2.0 million cells /mcl	02	04%
2.0 – 3.0 million cells /mcl	01	02%
Total	50	100%

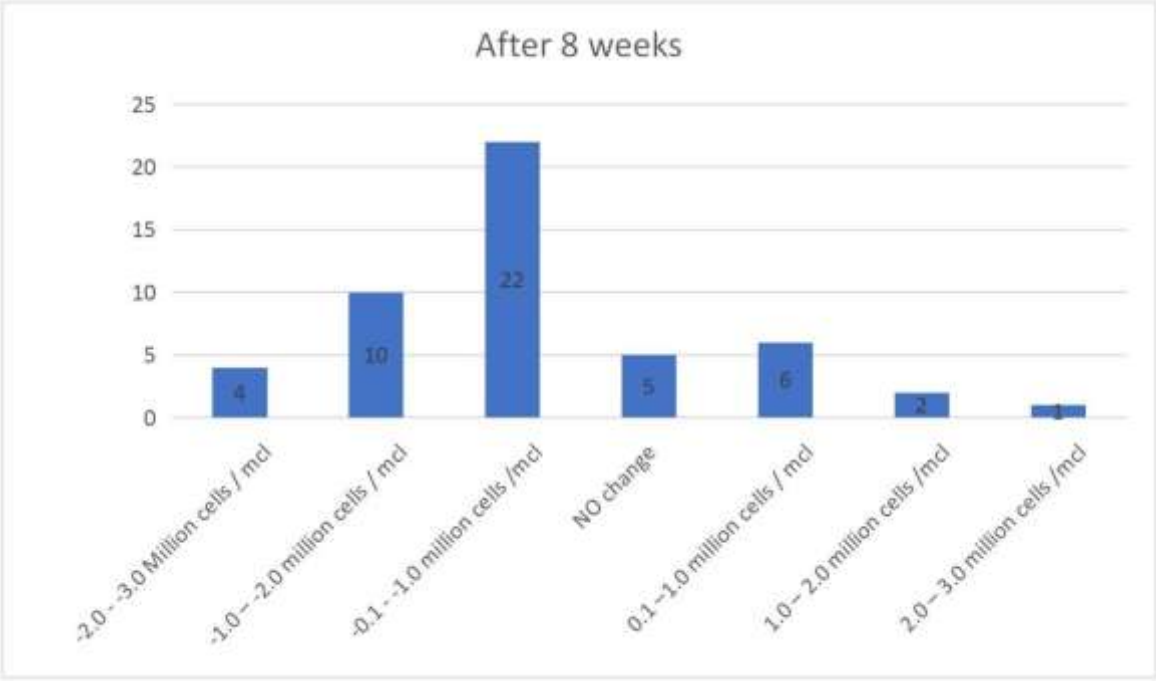


Table 31: Base line of WBC in patients in dapsone therapy

Out of 50 patients 08 patients had baseline WBC in range of(4,000- 6,000 cells/ ul), 08 patients had baseline WBC in range of (6,000- 8,000 cells / ul), 23 patients had baseline WBC in range of (8,000- 10,000 cells /ul), 8 patients had baseline WBC in range of(10,00012,000 cells /ul), 3 patients had baseline WBC in range of (12,000- 14,000cells /ul), 0 patients had baseline WBC in range of (14,000- 16,000 cells /ul).

BASELINE OF WBC	NO OF PATIENTS	Percentage
4,000- 6,000 cells /ul	08	16 %
6,000- 8,00 cells /ul	08	16%
8,000 –10,000 cells /ul	23	46%
10,000 – 12,000 cells /ul	08	16%
12,000 – 14,000 cells /ul	03	06%
14,000 – 16,000 cells /ul	00	0%
Total	50	100%

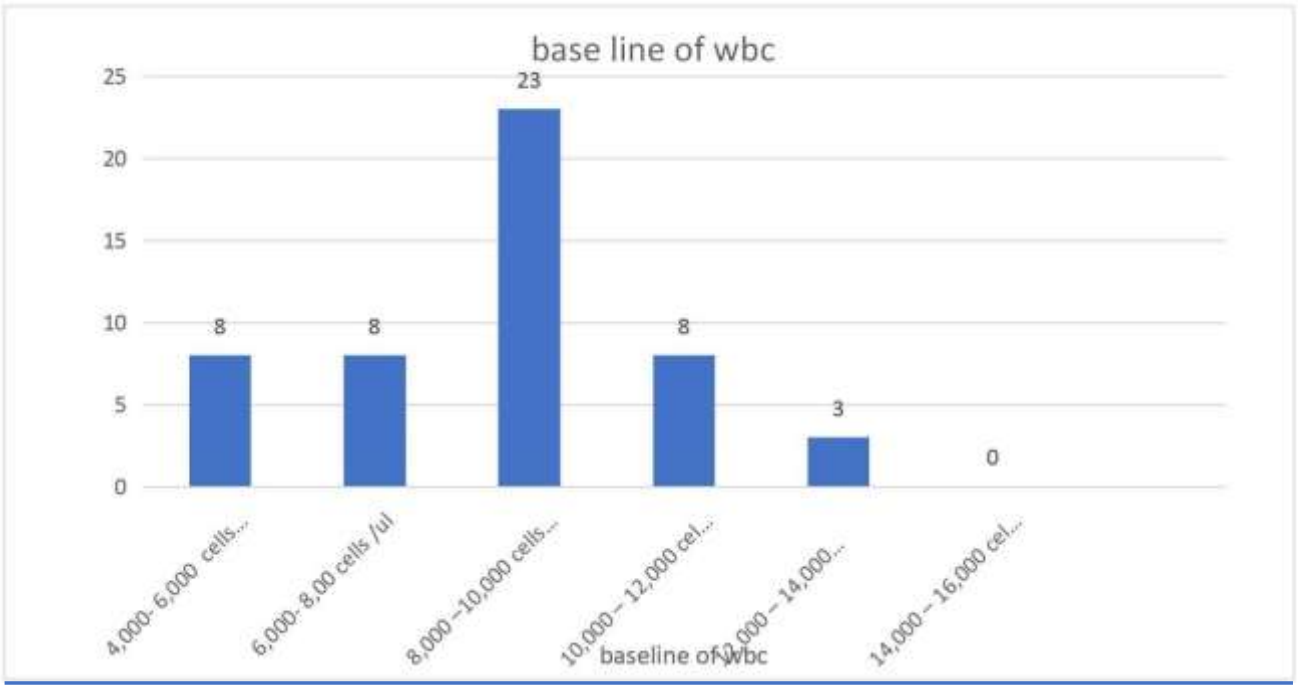


Table 32 :Changes from baseline after 2 weeks

Out of 50 patients 3 patient had no change WBC level at 2 months baseline , 26 patients had decrease in WBC level with 4 patients showing decrease by 24 gm %, 2 patients showing decrease by 4-6 gm %, 2 patients showing decrease by 6-8 gm %, 1 patients showing decrease by 8- 10 gm % ,17 patients showing less than 2 gm % . 21 patients had increase in haemoglobin level when compared to baseline , with 0 patients showing increase by 2- 4 gm %, 3 patients showing increase by 4-6 gm % , 0 patients showing increase by 6-8 gm %, 1 patients showing increase by 8- 10 gm %, 17 patients showing upto 1 gm %.

After 2 weeks	NO OF PATIENTS	Percentage
-8000—10000 microliter	01	2%
-6000--8000 microliter	02	4%
-4000- -6000microliter	02	4%
-4000- -2000 microliter	04	8%
-0 - -2000microliter	17	34%
No change	03	6%
1- 2000 microliter	17	34%
2000- 4000 microliter	00	0%
4000- 6000 microliter	03	6%
6000 – 8000 microliters	00	0%
8000- 10,000 microliter	01	2%
Total	50	100%

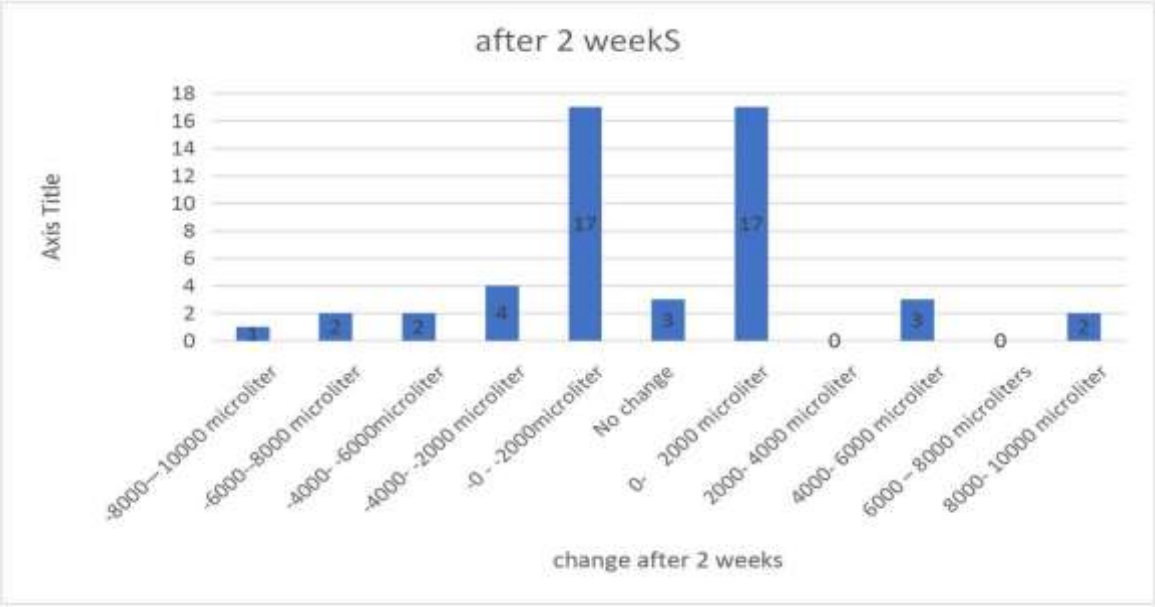


Table 33: Change from baseline after 4 weeks

Out of 50 patients 4 patient had no change WBC level at 4 weeks baseline , 27 patients had decrease in WBC level with 7 patients showing decrease by 2- 4 gm %, 3 patients showing decrease by 4-6 gm %, 1 patients showing decrease by 68 gm %, 3 patients showing decrease by 8- 10 gm % ,13 patients showing less than 2 gm % . 19 patients had increase in haemoglobin level when compared to baseline , with 2 patients showing increase by 2- 4 gm %, 1 patients showing increase by 4-6 gm % , 0 patients showing increase by 6-8 gm %, 2 patients showing increase by 8- 10 gm %, 14 patients showing upto 1 gm %.

After 4 weeks	NO OF PATIENTS	PERCENTAGE
-8000--10000microliter	03	06%
-6000--8000 microliter	01	02%
-4000- -6000microliter	03	06%
-4000- -2000 microliter	07	14%
-0 - -2000microliter	13	26%
No change	04	08%
1- 2000 microliter	14	28%
2000- 4000 microliter	02	04%
4000- 6000 microliter	01	02%
6000 – 8000 microliters	00	00%
8000- 10000 microliter	02	04%
Total	50	100%

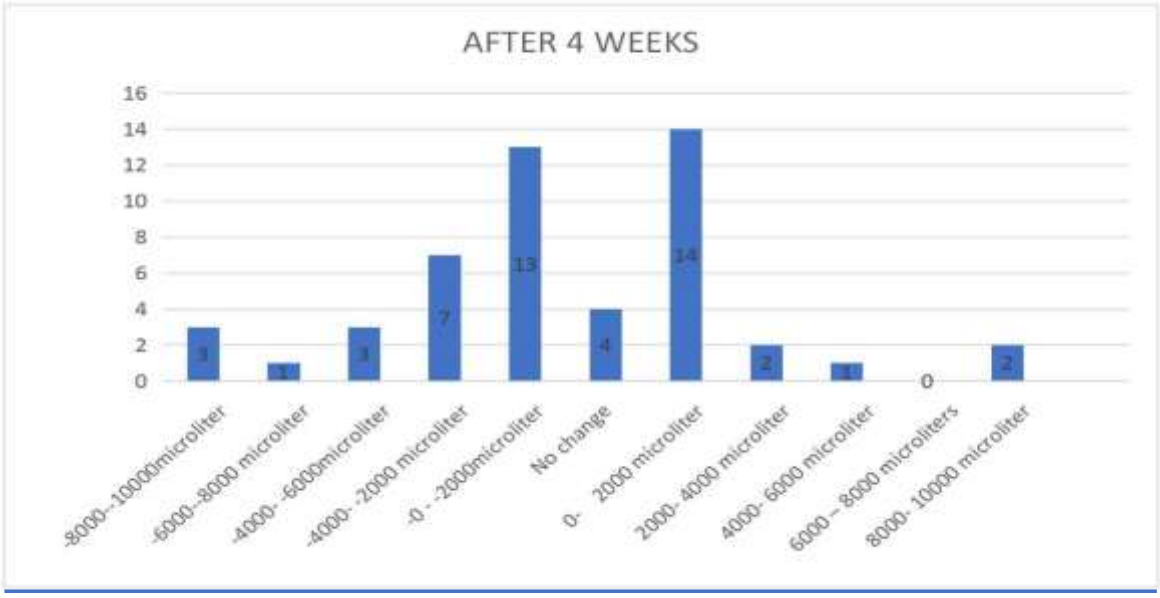


Table: 34: change from baseline after 8 weeks :

Out of 50 patients 2 patient had no change WBC level at 8 weeks baseline , 22 patients had decrease in WBC level with 6 patients showing decrease by 2- 4 gm %, 2 patients showing decrease by 4-6 gm %, 0 patients showing decrease by 68 gm %, 0 patients showing decrease by 8- 10 gm % ,14 patients showing less than 2 gm % . 26 patients had increase in haemoglobin level when compared to baseline , with 4 patients showing increase by 2- 4 gm %, 3 patients showing increase by 4-6 gm % , 1 patients showing increase by 6-8 gm %, 0 patients showing increase by 8- 10 gm% 18 patients showing up to 1 gm %.

After 2 months	NO OF Patients	Percentage
-8000--10000microliter	00	0 %
-6000--8000 microliter	00	0%
-4000- -6000microliter	02	4 %
-4000- -2000 microliter	06	12 %
-0 - -2000microliter	14	28 %
No change	02	4%
0- 2000 microliter	18	36%
2000- 4000 microliter	04	08%
4000- 6000 microliter	03	06%
6000 – 8000 microliters	01	02%
8000- 10000 microliter	00	0%
Total	50	100%

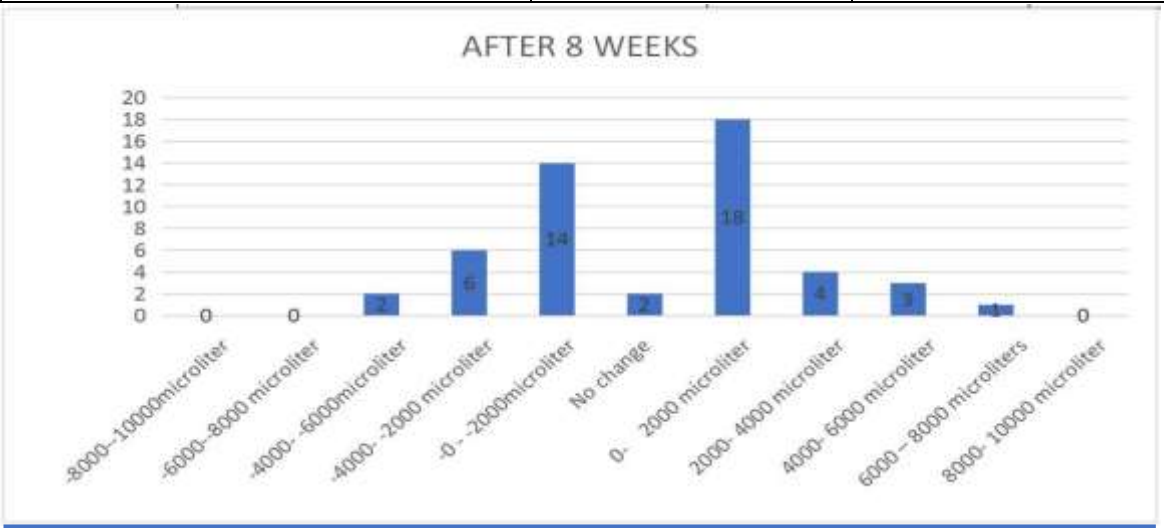


Table 35 :Baseline of in patients in dapsone therapy

Out of 50 patients 13 Patients had baseline platelet count in range of (1.5 – 2.5 lakh /ul) , 27 patients had baseline platelet count in range of (2.5 – 3.5lakh /ul), 07 patients had baseline platelet count in range of (3.5 – 4.5lakh /ul) , 3 patients had baseline platelet count in range of (4.5 – 5.0 lakh /ul).

Base line of platelet count	No of patients	Percentage
1.5 – 2.5lakh /ul	13	26 %
2.5 – 3.5 lakh /ul	27	44%
3.5 – 4.5 lakh/ul	7	14%
4.5 - 5.0 lakhs /ul	03	06%
Total	50	100 %

Table 36: Change from baseline after 2 weeks

Out of 50 patients 7 patients had no change platelet count at 2 weeks when compared to baseline ,24 patients had decrease in platelet count level with 4 patients showing decrease by 1- 2 gm %, 2 patients showing decrease by 2- 3 gm %, 17 patients showing less than 1 gm % decrease 21 patients had increase in haemoglobin level when compared to baseline , with 1 patients showing increase by 1-2 gm %, 0 patients showing increase by 2 – 3 gm % , 19 patients showing upto 1 gm %.

After 2 weeks	No of patients	Percentage
-2.0 - -3.0 lakh /ul	02	04 %
-1.0 – -2.0 lakh /ul	04	08%
-0.1 - -1.0 lakh /ul	17	34%
No change	07	14%
01 – 1.0 lakh /ul	19	38%
1.0 – 2.0 lakh /ul	01	02%
2.0 – 3.0 lakh /ul	00	0%
Total	50	100 %

Table 37: Change from baseline after 4 weeks

Out of 50 patients 3 patients had no change platelet count at 2 weeks when compared to baseline ,31 patients had decrease in platelet count level with 10 patients showing decrease by 1- 2 gm %, 2 patients showing decrease by 2- 3 gm %, 19 patients showing less than 1 gm 16 patients had increase in haemoglobin level when compared to baseline , with 2 patients showing increase by 1-2 gm %, 3 patients showing increase by 2 – 3 gm % , 11patients showing upto .1 gm %.

After 4 weeks	No of patients	Percentage
-2.0 - -3.0lakh /ul	02	4 %
-1.0 – -2.0 lakh /ul	10	20%
-0.1 - -1.0 lakh /ul	19	38%
No change	03	06%
01 – 1.0 lakh /ul	11	22%
1.0 – 2.0 lakh /ul	02	4%
2.0 – 3.0 lakh /ul	03	6%
Total	50	100 %

Table 38: Change in platelet count after8 weeks ::

➢ Out of 50 patients 5 patients had no change platelet count at 2 weeks when compared to baseline 28 patients had decrease in platelet count level with 4 patients showing decrease by 1- 2 gm %, 3 patients showing decrease by 2- 3 gm %, 20 patients showing less than 1 gm%, 17 patients had increase in haemoglobin level when compared to baseline , with 12 patients showing increase by 1-2 gm %, 1 patients showing increase by 2 – 3 gm % , 4 patients showing upto 1 gm %.

After 4 weeks	No of patients	Percentage
-2.0 - -3.0 lakh / ul	03	06%
-1.0 – -2.0 lakh /ul	04	08%
-0.1 - -1.0 lakh /ul	20	40%
No change	05	10%
01 – 1.0 lakh /ul	04	08%
1.0 – 2.0 lakh /ul	12	24%
2.0 – 3.0 lakh /ul	01	02%
Total	50	100%

DISCUSSION:

In this study a total of 100 patients were included with different morbidities, among them 50 patients were prescribed methotrexate and 50 patients were prescribed dapsone in outpatient department Sai Sudha hospital, Kakinada. All patients satisfying the inclusion and exclusion criteria were included as the study population.

The study duration was of 6 months.

In this study we analyses about hematological profile of patients on methotrexate and dapsone. In this study we observed almost equal usage of mtx in male (51.4 %)and female(48.6 %) .While evaluating the patients, most common indication for MTX was psoriasis(n=23, 46%) followed by exfoliative erythroderma(n= 4) (8%) , then PSS(n= 4, 8%) ,DLE(n= 4 , 8%), PPP (n=3 , 6%),SLE (n= 4 , 8%), ABCD (n =4, 8%) , lichen planus (n=2 , 4%) ,

In this study various age groups were included ranging from 21 years to 80 years and highest frequency of patients using methotrexate was seen in (51 – 60 years.)

- In this study we evaluated the hematological profile of patients on treatment with methotrexate where we mainly considered 4 main components - Hemoglobin, RBC, PLATELET COUNT and WBC.
- Hemogram values were recorded at baseline, 2 weeks, 4 weeks and8 weeks

In this study we observed that when compared to baseline 7 patients showed decreased levels of haemoglobin at 2 weeks, 8 patients showed decrease in the levels of HB at 4 weeks and 9 patients showed decrease in the levels of HB after 2 months

It proves the alteration of HB levels after taking MTX therapy.

In this study we observed that when compared to baseline 21 patients showed decreased levels of RBC at 2 weeks. 21 patients showed decreased levels of RBC at 4 weeks, 21 patients showed decreased levels of RBC at after 2 months.It proves the alteration of RBC levels after taking MTX therapy after 2 weeks. In this study we observed that when compared to baseline 19 patients showed increased levels of WBC in after 2 weeks 22 patients showed increased levels of WBC after 4 weeks and 23 patients showed decreased levels of WBC after 2 months.

It proves the alteration of WBC levels after taking MTX therapy

In this study we observed that when compared to baseline 15 patients showed increased levels of platelets in after 2 weeks, 19 patients showed increased levels of platelet count in after 4 weeks 21 patients showed increased levels of platelet count in after 2 months.

It proves the alteration of platelet count levels after taking MTX therapy

In this study we analyses about hematological profile of patients using dapsone.

- In this study we observed almost equal usage of dapsone in male (46 %)and female(54%)in study .While evaluating the patients most common indication for dapsone was lichen (n=26% Acne (n= 2 0 %) ,Hansen's disease (n = 10%) ,bullous pemphigoid (n = 10 %) , tropic ulcer (n= 10 %), pemphigus vulgaris (n= 10 %), chronic urticaria (n=4 %), LPP (n =4%), benechets disease (n-=2%) Several disease associated with dapsone therapy
- In this study various age groups were included in ranging from 21 years to 80 years and highest frequency of patients using dapsone was seen in (21- 30 years. In this study we evaluated the hematological profile of patients on treatment with dapsone components where we mainly considered 4 main components - Hemoglobin, RBC, PLATELET COUNT, WBC.
- Hemogram values were recorded at baseline ,2 weeks, 4 weeks and 2 months.

In this study we observed that when compared to base line 13 patients showed decreased levels of haemoglobin at 2 weeks, 13 patients showed decreased levels of HB at 4 weeks, 20 patients showed decreased the levels of HB after 2 months. It proves the alteration of HB levels after taking dapsone therapy.

In this study we observed that when compared to base line. 20 patients showed decreased levels of RBC at 2 weeks,17 patients showed decreased levels at after 4 weeks, 22 patients showed decrease levels of RBC at after 2 months.

It proves the alteration of RBC levels after taking dapsone therapy.

In this study we observed that when compared to base line 17 patients showed decreased levels of WBC at 2 weeks, 14 patients showed increase levels of WBC at after 4 weeks ,14 patients showed decreased levels of WBC at after 2 months It proves the alteration of WBC levels after taking dapsone therapy.

In this study we observed that when compared to base line 19 patients showed increased levels platelets at 2 weeks ,19 patients showed decreased levels of platelet count at after 4 weeks,20 patients showed decreased levels of platelet count at after 2 months.

It proves the alteration of platelet count levels after taking dapsone therapy.

CONCLUSION:

Methotrexate and dapsone are widely prescribed in modern medicine, forming a part of standard treatment for a wide range of dermatological disorders which include psoriasis. Acne and bullous pemphigoid. Apart from their beneficial effects they produce number of adverse effects.

In this study, we monitored the hematological profile of patients using methotrexate and dapsone most of the patients had anemia. Other adverse effects like Oral candidiasis, Cutaneous adverse effects like rashes were reported. Some of the patients showed only one adverse effect while others showed more than one (due to higher dose of drugs).

Till now, effective treatment guidelines for methotrexate and dapsone are not available. Even though we can't completely eliminate the occurrence of ADRs, we can definitely it.

To ensure safety, efficacy and well-balanced therapeutic management with methotrexate and dapsone, both patients and prescribers should be more aware of the appropriate dose, dosage regimen, and drug-drug interactions. The clinical pharmacist can perform potential role in health care system in assisting physician in altering the number of medications taken, the number of doses taken, improving the patient medication adherence, preventing the adverse drug reactions, drug-drug interactions, in patient counselling, improves the health-related quality of life and decreases the health care cost of the patient.

The major study findings in our study includes: □ In our study
equal usage of drugs in male and female **Methotrexate:**

- TAB METHOTREXTATE was mostly used in (51-60) **age** group.
- Methotrexate was mostly prescribed in patient with Psoriasis, Erythroderma, DLE

- 60 % increase in HB % levels in methotrexate therapy
- 50 % increase in RBC levels in methotrexate therapy 50 % increase in WBC levels in methotrexate therapy 60 % increase in platelet levels in methotrexate therapy.
- No significant found in HB / megablastic anemia
- No significant found in RBC / anemia
- No significant found in WBC /leukopenia
- No significant found in platelet / thrombocytopenia
- No major life-threatening disease found in methotrexate therapy

DAPSONE :

- TAB DAPSONE was mostly used in (21 – 30) age group
- Dapsone was mostly prescribed in patients of Hansen's disease, acne, pemphigus vulgaris, bullous pemphigoid.
- 80 % decrease in HB % levels in dapsone therapy
- 60 % decrease in RBC level in dapsone therapy
- 50 % decrease in WBC level in dapsone therapy 68 % decrease in platelet levels in dapsone therapy .

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